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ORIGINAL ARTICLES

FACTORS MODIFYING THE DURATION OF VENTRICULAR SYSTOLE*

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I. INTRODUCTION

THE maintenance of an adequate circulation of blood, which is primarily the function of the heart, is accomplished chiefly by the rhythmic activity of the ventricles. Each ventricle operates as a pump, expelling blood by the contraction of its muscles during the phase known as systole and refilling its chamber from the auricle during the phase known as diastole. Although emphasis has been laid on the fact that the circulating minute volume and the systolic and diastolic blood pressures are dependent on the systolic discharge and the rate of the heart, it has not always been appreciated that these must also be considerably affected by the *duration* of the systolic discharge as related to the diastolic time allowed for refilling. The question at once arises as to how much the duration of systole can vary and what factors operate to cause these variations. A critical consideration of the literature and the results of this investigation are presented in this paper in an attempt to answer this question, not only because of its scientific import but also for the practical bearing it may have on the clinical study of the heart.

The heart cycle is divided into systole, or that period during which the ventricular muscle is either mechanically shortening or increasing its tension, and diastole, or that portion of the cardiac cycle between the end of one systole and the beginning of the next. Systole can be further subdivided into an isometric and an ejection period.[20] The isometric period, which begins with the contraction of the ventricle, is so termed because the heart contracts without any change in length. During this period, the ventricle is entirely shut off from the other chambers except for a brief interval at the onset. No blood is therfore expelled from it until the semilunar valves open. The opening of these valves marks the begin-

*This thesis, awarded the prize offered by the Alpha of Ohio chapter of the Alpha Omega Alpha for 1920, has been somewhat condensed for publication and only the more necessary illustrations have been retained. A detailed report of that part of the work concerning the selective influence of the accelerator nerves has already been published in association with Wiggers in the American Journal of Physiology, 1920, liii, 49.

ning of the ejection phase, during which the ventricle contracts tonically and ejects the blood in it into the aorta (or pulmonary conus) with which it then communicates.

Diastole can also be subdivided into a period of rapid diastole, a period of diastasis and a period of auricular activity. The period of rapid diastole begins with the relaxation of the ventricle and lasts a variable time. The ventricle, during the early part of this phase, except for an extremely short interval at the onset, is a closed chamber and no blood enters. Later, however, when the auriculo-ventricular valves open, the ventricle fills with blood from the auricle. The filling of the ventricle continues during the next phase also, but at a much slower rate. This period is termed the period of diastasis as in it the ventricular muscle has reached a stage of rest. Toward the end of this phase another impulse, arising in the sinus node, sets up an auricular contraction, fractionate in character,[56] which constitutes the period of auricular activity. There is still some dispute as to what rôle the auricular activity plays in the filling of the ventricle.[1, 2, 9, 17, 18, 20] The time relation of these various events in the cardiac cycle is well illustrated in Fig. 25 of Wiggers' Monograph.[20]

II. METHODS OF DETERMINING THE DURATION OF SYSTOLE

The value of the conclusion of any research depends as much on the efficiency of the method employed as on the interpretation of the observations. For this reason a brief survey of the methods available for temporal studies of the cardiac phases is presented.

Any of the changes or combinations of changes that accompany the heart cycle may be utilized to determine the duration of systole. These changes of the heart cycle can be studied in (1) the myocardiograph, (2) the volume curve, (3) the intraventricular, intraauricular and intraaortic pressure curves, (4) the apex beat, (5) the venous pulse, (6) the arterial pulse, both central and peripheral, (7) the electrocardiograph and (8) the heart sounds.

An objection raised to many of these records is that they do not actually measure the entire duration of systole. Thus the myocardiograph, the volume curve and the arterial and venous pulse curves do not record the isometric period, and the results obtained from them must be interpreted as referring only to the ejection period. The electrocardiographic records which have been utilized [25, 30, 50, 53] to determine the duration of ventricular activity are also unreliable for this purpose. The significance of the various deflections are not as yet settled so that the results obtained cannot at the present time be properly interpreted (see Hewlett,[8] Macleod,[12] Wiggers.[20]) Observations which are obtained from graphically recorded curves are also objected to for, due to the short duration of systole, the error introduced in these curves by the recording levers through friction, inertia and momentum is sufficient to lead to erroneous results. Similarly results obtained with some of the membrane manometers, such as Hurthle[40] and Hunt[42] used, are also inaccurate and unreliable (Frank[34]).

For one or other of the above reasons most of the methods mentioned are unsuitable for *accurate* and *exacting* studies of the duration of the heart phases. Those which do not require the opening of the chest, however, can be used for ordinary clinical purposes.

The most accurate and definite estimation of systole can be obtained from a simultaneous tracing of the optically recorded intraventricular and aortic pressure curves, measuring from the beginning of the rise of pressure in the ventricular to the beginning of the incisura of the aortic curve. The objection to such a method lies in the necessity of opening the chest. The circulation under these circumstances is far from normal, due to the shock of the operation as well as the bleeding which occurs even with the best technic.[57] The necessity of deeper anesthesia, the replacement of the negative intrathoracic by atmospheric pressure, the cessation of natural respiration and the utilization of artificial respiration, all aid in making the circulation abnormal.

An attempt was made to select for this investigation that procedure which permits an accurate and exact estimate of the duration of systole and diastole while *still keeping the circulation normal.* The most satisfactory method answering these prerequisites is obtained by recording the heart sounds. Wiggers and Dean[60] have shown that the main vibrations of the first sound, when recorded directly from the heart, begin with the rise of the intraventricular pressure and that the beginning of the second sound coincides with the beginning of the fall of the incisura. These records therefore compare favorably with the simultaneous records of the intraventricular and aortic pressure curves, as to accuracy and definiteness, and have the added advantage of not necessitating the opening of the chest.

Heart sounds have been variously recorded.[7, 22, 41] At the present time there are two generally accepted procedures. In one the heart sounds are registered electrically by means of a microphone connected to a string galvanometer, as is the case in Einthoven's phonocardiograph,[21, 29, 32, 45] The other method records the heart sounds by means of capsules and air transmission.[20] This method has recently been perfected by Wiggers and Dean[60] and has been successfully used to record murmurs and the intensity of the sounds.[58, 59] The clear cut records obtained by this last method were used in this research.

III. PROCEDURE OF INVESTIGATION

(*a*) *Animals and Anesthesia*: Dogs, the animals used, were put under the influence of chloretone and morphine, which gives a lasting anesthesia.

(*b*) *Operative Procedures*: In addition to the ordinary procedures, namely tracheotomy, vagotomy, the insertion of cannulæ into the carotid artery and jugular vein, the stellate ganglion was exposed without resecting any ribs.

The operation performed is very similar to the one first described by Schmeideberg.[4] The animal, during the operation, was kept on a board warmed by electric bulbs. The skin incision, used for the tracheotomy was prolonged to the sternum and then carried at right angles to the end of the shoulder girdle. The skin was next reflected so as to expose the muscular and the subclavian triangles of the neck. The sternomastoid, sternohyoid and sternothyroid muscles were divided close to their insertion into the sternum, pulled back and the vessels beneath them exposed. The pectorales were also divided for half an inch near their sternal end so as to expose the subclavian vessels. The large veins at the root of the neck on one side were dissected out and a ligature tied to each near its entrance into the mediastinum. Another ligature was placed some distance

up and the branches entering between them tied off. The vein between these two ligatures was then resected. The arteries were ligated and removed in a similar manner. In tying the subclavian artery special care was taken not to injure the ansa subclaviae.

After the vessels were tied the previously exposed vagus was dissected free until the branches going to the inferior cervical ganglion were exposed and followed to this ganglion. The esophagus and trachea were then drawn toward the opposite side and by following the branches of this ganglion that proceed posteriorly, medially, and caudad the stellate ganglion, which lies about the junction of the first rib with the vertebral column, posterior to the esophagus, was exposed.[26]

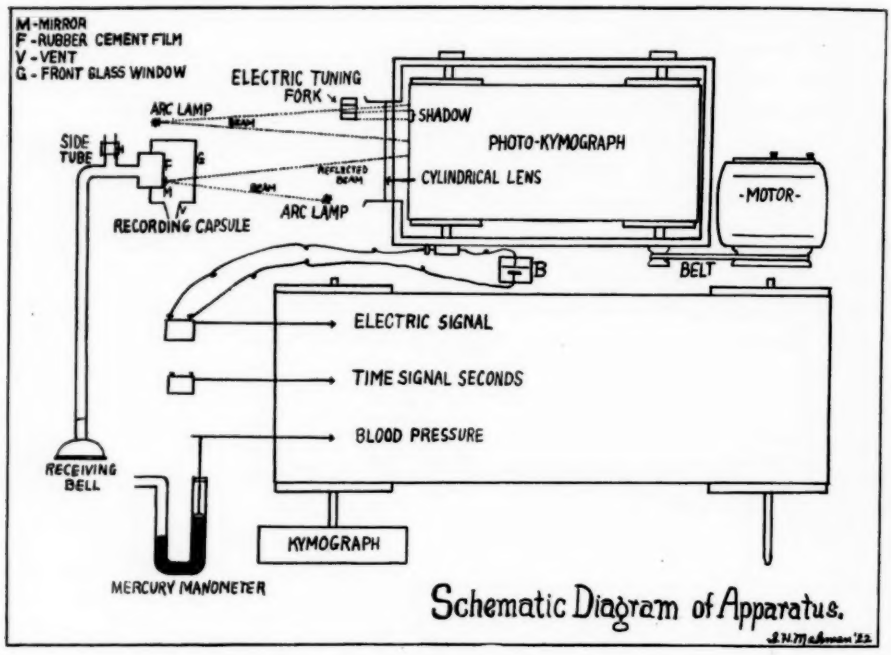

Fig. 1.—Schematic diagram of apparatus used. Description in text.

Some difficulty was occasionally experienced in the last part of the operation until the vertebral vessels, which ordinarily can be pushed aside, were ligated and removed. In working at the root of the neck care was taken not to injure the pleura or the nerves, to tie the ligatures on the vessels tightly so as to prevent hemorrhage or air embolism, and to reduce shock to a minimum. In this way an animal with a practically normal circulation was available.

(*c*) *Apparatus*: A diagrammatic representation of the apparatus is given in Fig. 1. On a long smoked kymograph, a continuous record of blood pressure was taken by means of a mercury manometer, the time was given by a time-signal recording in seconds. An electric signal was connected to the photokymograph so that it recorded on the smoked drum when and how much of the optical tracing was taken. In addition the signal also served as a base line for the blood pressure. The apparatus for recording the heart sounds is also represented in

Fig. 1. The sounds were picked up from the desired areas by means of a stethoscope bell which was strapped with an elastic belt to the previously shaved chest. The sounds were transmitted to a capsule through a soft rubber tube, which had a side opening to eliminate the cruder variations of pressure, such as the apex beat. The sounds caused the rubber film stretched over the capsule to vibrate. Extraneous sounds were prevented from affecting this membrane by enclosing the capsule in a housing with a window to permit a beam of light through and a vent to equalize the pressures on both sides of the film. A beam of light from an arc lamp was focused on the mirror supported by the film, so that the reflected beam passed through the slot of a photokymograph,[57] which consists essentially of rollers so arranged in a closed box that the bromide paper, rolled up on one of them, moves past a slot and is rolled up on another. To establish time relations the shadow of a tuning fork vibrating fifty times per second was photographed simultaneously with the heart sounds. A typical record thus obtained is shown in Fig. 2.

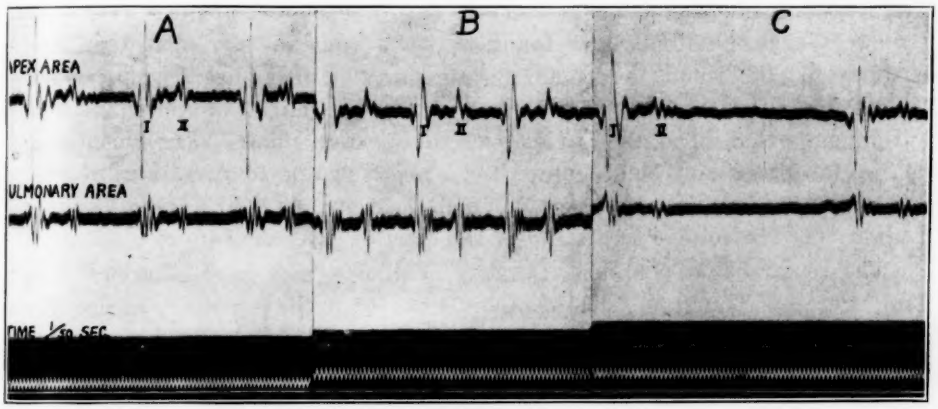

Fig. 2.—Optical records of heart sound (in dog) obtained by direct method (½ actual size). A, under normal conditions of anesthesia; B, during stimulation of right stellate ganglion; C, during vagus stimulation. Illustrating the relative alterations of systole and diastole during the action of the two nerves.

(*d*) *Procedure:* The sounds were recorded during consecutive beats in the following experimental conditions. Vagi intact:

1. During normal action of the heart under anesthesia (called normal standard);
2. During stimulation of the stellate ganglion;
3. During action of pituitary extract before, during and after stimulation of the accelerator nerve;
4. Following section of both vagi.

After section of the vagi:

5. During stimulation of the peripheral end of the vagi;
6. During stimulation of the stellate ganglion;
7. During action of epinephrin;
8. During the injection of saline intravenously;
9. During compression of the abdominal aorta.

The records so obtained were developed and the systole and cycle lengths measured. The error introduced in measuring the records is about 0.002 seconds. In all, some three thousand heart cycles were measured and tabulated.

IV. A REVIEW OF THE LITERATURE CONCERNING THE INFLUENCES MODIFYING THE DURATION OF SYSTOLE AND DIASTOLE

It is common knowledge that the duration of diastole is very variable, but the fact that systole varies is often lost sight of. The duration of systole may be altered when the duration of either the isometric or the ejection period is changed. This may conceivably be produced by (*a*) mechanical influences modifying the conditions under which the heart pumps, and (*b*) nerves, chemicals, etc., presumably altering the physiologic properties of the heart muscle.

(*a*) *Mechanical Factors*: Theoretically it may be supposed that the duration of the isometric period of systole might change readily. Thus it may be argued that an increase in initial ventricular pressure or a decrease in aortic resistance tends to shorten the isometric period, for it does not take as long for the ventricular pressure to exceed that of the aorta. There is no experimental evidence, however, that variations of the isometric period do play a great part in determining the duration of systole. Thus, Hurthle,[40] de Heer,[38] Garten[37] and Frank[33] found this period fairly constant and independent of heart rate. More recently Wiggers and Clough[61] found that the isometric period in man varies from 0.04 to 0.06 seconds independent of the duration of the heart cycle or systole. The duration of systole must therefore be largely determined in a mechanical way by influences that effect the duration of the ejection phase. The variations of the ejection phase may be accounted for *a priori* as due to alterations of one or more of three variables: (1) the volume of the ventricle at the beginning of the ejection; (2) the volume at the end of the ejection; (3) the rate of ejection.

The researches of Landois, Donders, Volkman,[7] and later Edgren,[27] Chapman,[24] Porter,[52] Thurston,[54] among others, have led to the commonly accepted conclusion that the main changes with heart rate occur in diastole. That systole varies with heart rate has also been demonstrated [see Curtiss,[3] Foster,[5] Hart,[6] Landois and Sterling,[10] Rollet,[7] Hill,[15] Tigerstedt[19] and Wiggers,[20] (table, p. 41)]. More recently, Wiggers and Clough[61] found that, in man, systole varies from 0.25 to 0.30 seconds for heart rates of 66 to 100, and Lombard and Cope (results as yet unpublished) noted a variation of systole from 0.236 to 0.290 seconds when the heart rate varies from 66 to 89.

Several attempts have been made to correlate the systolic duration with heart rate. Thus, to establish such a correlation Garrod[36] has presented two formulæ which he calculated from the cardiogram and radial pulse. For the former he offered the formula $xy = 20\sqrt{x}$; for the latter $xy = 47\sqrt[3]{x}$. In both x is the heart rate per minute, y the relation of systole to cycle length. Later Lombard and Cope[46, 47] presented the formula $S = \frac{60}{K\sqrt{R}}$ to determine the length of systole from heart rate, S being the duration of systole, R the heart rate per minute and K a constant varying for position of body, etc. They used the carotid pulse to obtain their data. K, they found, varied as the patients were lying down, sitting up or standing.

Another attempt to correlate the duration of systole to heart rate may be based on Henderson's volume curves. In 1906, and later in 1909, Henderson[39] promulgated the law of Uniformity of Behavior of the heart. This law maintains that at different heart rates the amplitude but not the contour of the ventricular

volume curve is modified. Henderson found that because the effective venous pressure is normally greater than the critical, the volume curves of the ventricle are superimposable on the curve of a vagus beat (Fig. 3). He further maintained that in accordance with his law, the separate functions of the heart, which Engleman[31] claimed can change independently, vary only with the heart rate. It is evident from his curve that changes in duration of systole with heart rate occur mainly by alteration of the volume of the ventricle at the beginning of systole (Fig. 3). Using his published curve and plotting the temporal relations of systole to cycle (after adding 0.05 seconds for the isometric period) it was found that, until the cycle became less than 0.7 seconds, systole was practically constant. With shortening of the cycle beyond this, however, systole shortened progressively (see Fig. 5).

The heart rate is not the only influence that modifies the duration of systole. Other mechanical influences have been found to do this. Thus, Bowen[23] in 1904 found that systole is prolonged in man at the beginning of exercise before the

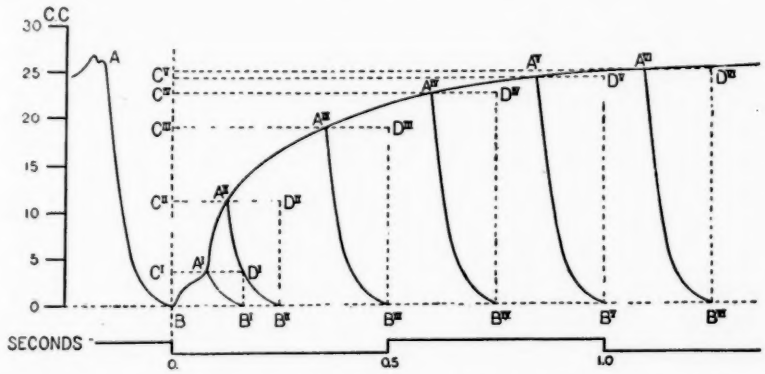

Fig. 3.—Standard volume curve (from Henderson). C'D' and BB', etc., is the duration of the heart cycle; C'A', etc., is the duration of diastole; A'D', etc., is the duration of the ejection period.

nerves could compensate. Patterson, Piper and Starling[51] in 1914 found that when nerve influences are removed an increase in arterial resistance or in venous return increases the duration of the entire systole. They used their heart-lung preparations to obtain these results. The increase of the diastolic volume of the ventricle, they asserted, is the cause of lengthening of systole. Both the diastolic volume and the volume of the ventricle at the end of systole are altered by changes in arterial resistance or venous flow. They concluded, that in a heart removed from extrinsic nervous influences, these factors could alter the duration of systole independent of the heart rate.

(*b*) *Influences Other than Mechanical*: Chemicals, as for instance calcium, sodium and potassium ions, have been shown to modify the duration of systole.[16] Temperature likewise modifies the duration of systole as Langendorf[44] has demonstrated.

The cardiac nerves have been thought to have a similar effect. A detailed review of the literature concerning the effect of these nerves on the duration of systole and diastole is given in a recent paper with Wiggers[62] and therefore only a brief summary is presented here. The fact that the vagi and accelerator nerves

modify the heart rate has been known since their discovery by the Weber brothers, Cyon brothers and V. Bering.[13] At the present time it is almost universally accepted that they are the main factors involved. It has also been accepted that the vagi depress all of the heart's functions while the accelerators stimulate them[13] and that these nerves are tonically active,[42] the former being more powerful than the latter.

The work of Baxt,[22] Klug,[43] MacWilliam,[49] V. Frey and Krehl,[55] Hurthle,[40] Frank,[35] Hunt[42] and Patterson, Piper and Starling,[51] led these investigators to the conclusion that the vagi chiefly affect the duration of diastole while the accelerators mainly alter the duration of systole. Henderson,[39] however, maintained that there is no such difference, the nerves altering the heart rate primarily and the volume curves obtained during their stimulation being superimposable. The results of previous workers are however quite explainable by Henderson's uniformity of behavior conception. The ratio of systolic duration to cycle length calculated from his curve (Fig. 3) shows that in the shorter cycles, which stimulation of the accelerators would give, more marked changes in systole occur than in the longer cycles such as are obtained by stimulation of the vagus. From the literature, therefore, it is difficult to be sure whether the nerves act only by altering the heart rate and that the other changes follow Henderson's law, or whether they have in addition a direct influence on the inherent irritability and contractility of the ventricular muscle.

V. RESULTS—THE VARIATIONS OF THE DURATION OF SYSTOLE AND DIASTOLE UNDER DIFFERENT CARDIOVASCULAR CONDITIONS

1. *Natural Variations of Systole and Diastole from Beat to Beat.*—It has been previously recognized that in man systole and diastole undergo variations from beat to beat.[48] In fact Lombard and Cope noted that rhythmic alterations of these phases occurred synchronous with the respiratory and vasomotor changes. No attempt was made in the present report to enter into the detailed relation of the heart's phases to these phenomena. It was found, however, that in anesthetized dogs, under natural conditions, variations occur during consecutive cycles. The greatest and smallest values in 10-15 such cycles were tabulated in a few experiments (Table I). It is evident from this table that, as in man, diastole is more variable than systole. Dogs with the more rapid heart rate (animals 1, 2, 3) show less variation in the duration of diastole than those with longer cycles (animals 4, 5, 6) although systolic variations are about the same in both. It may be supposed that in these "short cycle" dogs the accelerator-vagus balance, in the sense of Reid Hunt,[42] is thrown over to the accelerator side because of a diminished vagus tone.

TABLE I

THE VARIATIONS OF SYSTOLE AND DIASTOLE FROM BEAT TO BEAT UNDER STANDARD CONDITIONS*

ANIMAL	SYSTOLE	DIASTOLE	VARIATIONS IN SYSTOLE	VARIATIONS IN DIASTOLE
1	.137-.145	.175-.192	.008	.017
2	.152-.165	.177-.192	.013	.015
3	.200-.210	.205-.217	.010	.012
4	.222-.227	.325-.350	.005	.025
5	.235-.250	.335-.385	.015	.060
6	.257-.262	.357-.410	.005	.053

*In this, as in the following tables, representative cycles only are given for clarity.

After section of the vagi some variations of both systole and diastole still occur, as is illustrated in Table II, showing that the vagi are not the only influences rhythmically affecting the phases of the cardiac cycle. This suggests that normally, in addition to the vagus tone, some other tonic cardiac influences, such as the accelerator nerves, or some of the physical conditions associated with the contraction of the heart, are able to control the temporal variations of systole and diastole.

This conclusion is further indicated on studying the relation of systolic to diastolic variations. Thus, Lombard and Cope[48] recently found that in man the variations of these phases, as they measured them, were neither synchronous nor of like degree.

TABLE II

THE VARIATIONS OF SYSTOLE AND DIASTOLE FROM BEAT TO BEAT AFTER THE VAGI WERE CUT.

ANIMAL	SYSTOLE	DIASTOLE	VARIATIONS IN SYSTOLE	VARIATIONS IN DIASTOLE
1	.117-.135	.160-.177	.018	.017
2	.127-.137	.142-.167	.010	.025
3	.180-.200	.180-.197	.020	.017
4	.202-.215	.285-.297	.013	.012
5	.215-.220	.340-.357	.005	.017
6	.247-.257	.292-.327	.010	.035

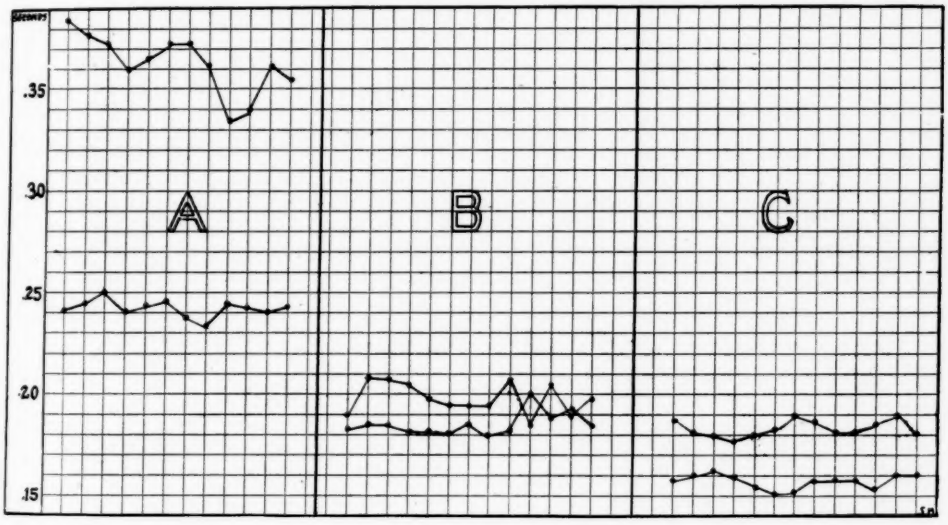

Fig. 4.—The relation of systole to the preceding diastole under natural conditions, each systole plotted as a dot vertically below its preceding diastole. Upper plot diastole, lower plot systole. A, B, C—from three different animals.

In studying the relation of these two phases, it was found more advantageous in this investigation to compare the duration of systole with the *preceding* diastole rather than with the one that follows. In this way one can determine whether systole varies independently of diastole or whether it follows the changes induced in the phase preceding it. No constant relation was found on carrying out this comparison in a number of experiments as the results of a few experiments illustrated in Fig. 4 show. These observations demonstrate that the variations of systole are not entirely determined by variations of diastole occa-

sioned by changing vagus tone. Although the variations are slight, yet often the alteration in systole is in the same direction as that of the following rather than the preceding diastole being in the opposite direction to the latter. It follows from this that in some cases at least the influence that causes the variation acts directly on systole (Fig. 4).

2. *Relation of the Duration of Systole to Heart Rate under Natural Conditions.*—A number of attempts have been made to show that a definite, or at any rate an average systole, normally occurs for any given heart rate. Lombard and Cope's formula, alluded to above, is an attempt to effect such a correlation in man. It is interesting to apply this formula to dogs and check its reliability. This was attempted in Fig. 5 where the actual $\frac{\text{systole}}{\text{cycle}}$ ratio (the ratio of systolic duration to cycle length) of the various animals under standard conditions is compared with the ratio calculated from Lombard and Cope's formula.

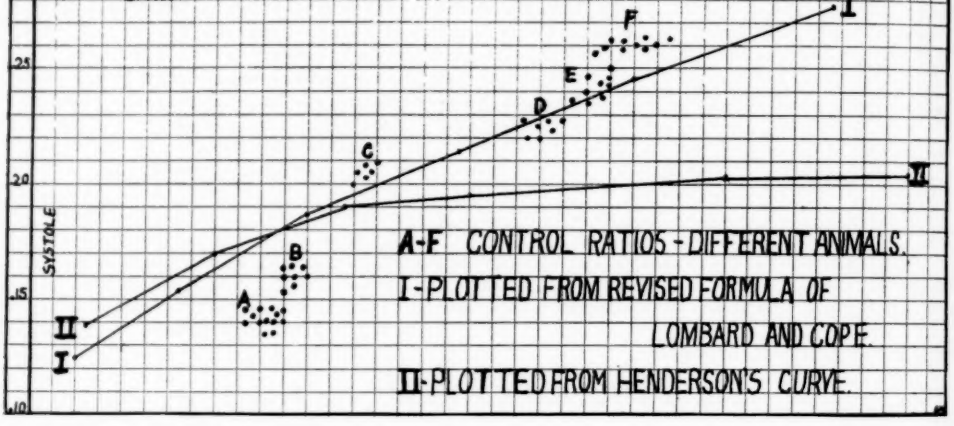

Fig. 5.—The relation of the normal systole-cycle ratio of several dogs, as compared with the curve plotted from Lombard and Cope's revised formula, ($S = .31\sqrt{c}$) and with the curve plotted from Henderson's published curve (adding 0.05 sec. for the isometric period).

Inasmuch as such a plot involves the use of cycle length, whereas Lombard and Cope used heart rate, their formula was revised here by substituting C (cycle length) for R. It is obvious that the heart rate is the reciprocal of the cycle length. This may be expressed by the equation R (heart rate per minute) $= \frac{60}{C}$ (cycle length in seconds) On substituting $\frac{60}{C}$ for R, their formula $S = \frac{60}{K\sqrt{R}}$ is changed to $S = \frac{60}{K\sqrt{\frac{60}{C}}}$. To simplify this both sides of the equation are first squared $S^2 = \frac{60^2}{K^2 \frac{60}{C}}$ or $\frac{60\,C}{K^2}$ resulting. Extracting the square root of this last equation changes it to $S = \frac{\sqrt{60C}}{K}$ or approximately $S = \frac{7.8\sqrt{C}}{K}$. Since K for the recumbent position is 25 the equation can be further simplified

to $S = .31\sqrt{C}$. It is evident from the plot (Fig. 5) that Lombard and Cope's formula holds fairly accurately in dogs whose heart rate is less than 150 per minute. In the more rapid rates, however, the systole-cycle ratio actually found falls short of that calculated from their formula. This indicates that although such formulæ may be very valuable in calculations for which they are intended, yet it is difficult to evolve a formula that will take cognizance of all conditions and be applicable without limit.

Another attempt to relate systole and cycle length may be founded on the standard volume curve of Henderson (Fig. 3). This was attempted as illustrated in Fig. 5, where the actual systole-cycle ratios of several dogs under standard conditions were compared with the ratio calculated from Henderson's published curve. The plot shows that the actual results do not agree with the ratio calculated from his curve, making it obvious that the standard volume curve of one animal is not applicable to another. To establish a theoretical systole-cycle ratio with which to compare the actual results it is therefore necessary to construct a standard curve for each animal. A detailed and illustrated presentation of the manner of constructing such a curve has already been published with Wiggers.[62] A brief outline of the method may, however, be presented here. A long vagal beat, occurring after slowing has been established for some time, is selected. From it the duration of its ejection period is determined and laid off on the abscissa of a large-sized coordinate paper. An arc, similar in contour to that given in Henderson's curve, is drawn to fill in this time. At one second intervals on the abscissæ, segments of arcs of the same contour and parallel to the ejection curves are erected. The duration of the ejection periods at different cycle lengths and for different filling curves are then determined and from these a curve of systole-cycle ratios is plotted as the standard for comparisons in that animal.

3. *Relation of Consecutive Systolic and Diastolic Durations when the Cardiovascular Conditions are in the Process of Changing.* (*a*) *Relation During Changing Heart Rate*: It is interesting to further determine how the duration of systole and diastole alter with changing heart rate. The experiments performed in this research show that when the heart rate increases from a slow to a more natural rhythm, such as occurs in the recovery from vagus stimulation, (Fig. 6), the period of diastole shortens below *normal* in a short time. Systole however does not decrease so rapidly and reaches normal somewhat later. Again, when the heart rate changes from a rapid to a more natural rate, such as occurs after the cessation of accelerator stimulation (Fig. 6) diastole immediately increases above the *normal* duration while systole may not return to its former duration until twenty-five seconds later. These observations suggest that during the alteration of heart rate the duration of diastole is affected first. However, when the accelerators act as during the beginning of epinephrin action (Fig. 6) and during the early part of electrical stimulation of these nerves, systole is occasionally, but not always, shortened first.

It is obvious from these observations that, because of a lack of a constant relation between systole and diastole, the systole-cycle ratio will vary, depending on whether cycles are taken during the early or later stages of a change. It is

during these periods of changing heart rate that cycles which deviate noticeably from Henderson's law of Uniformity of Behavior are found.

In a later section of this report the temporal changes produced by stimulation of the vagi and accelerator nerves will be analyzed. There are, however, noticeable differences when such stimulation ceases. Thus, after the vagus has ceased to act, the heart rate—which is inversely proportional to cycle length—quickens for a time beyond normal, as pointed out above. This is explainable either on Gaskell's hypothesis[15] that the vagi are anabolic and have caused an excess of energy to be stored up or that their normal tone is lost, due to the exhaustion from the stimulation. The lagging of systole can be further explained by the increase in diastolic volume of the ventricle due to the decreased minute output occurring during the stimulation. The increase of diastolic volume outlasts the stimulation and this will maintain the increased duration of systole.[51] As the rate becomes more rapid and the minute output again in-

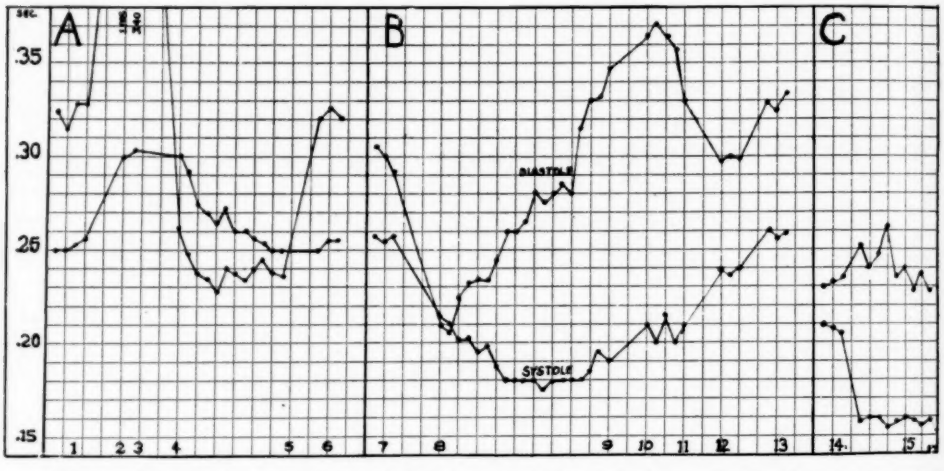

Fig. 6.—The variations of systole and diastole: A—during and after vagus stimulation; B—during and after accelerator stimulation; C—during the action of epinephrin. 1—control; 2-3—during vagus action; 3—vagus stimulation ceased; 3-4—six beats omitted; 4-5—after cessation of vagus stimulation; 6—control; 7—control; 8—the 58th beat after onset of accelerator stimulation; 9—stimulation ceased; 9-10—ten beats omitted; 11-12—35 beats omitted; 10-11, 12—after cessation of accelerator stimulation; 13—control; 14—control; 15—early during the action of epinephrin.

creases, the diastolic volume returns to normal and, as a result, systole again becomes of normal duration.

When considering the results of recovery from the accelerator stimulation, pointed out above, the slowing of the rate beyond normal can be explained by assuming that these nerves are catabolic,[15] or that the stimulation has exhausted them and so removed their normal tonicity. The marked lagging of systole indicates that, in addition to the influence of changing diastolic volume, there must be some specific effect on the heart muscle by these nerves. The more prompt effect on systole sometimes produced by epinephrin and by stimulation of the accelerators, pointed out above, is further evidence for this conclusion.

(*b*) *Relation During Changing Venous Pressure*: Temporary variations of the duration of systole which occur with changing heart rate may also appear during the modification of other cardiovascular influences, such, for example, as the venous pressure. The changes occurring during increasing venous pres-

sure can be readily produced by a rapid intravenous injection of saline. This was done in a number of experiments after the vagi were sectioned and the variations during and after the injection determined. The results of one such experiment, typical of all, is illustrated in Fig. 7. From this figure it will be seen that the changes produced vary, depending on how soon after the injection the cycles are taken. Thus, the sudden increase in venous return first causes a prolongation of systole and a decrease in the duration of diastole, the heart rate remaining unaltered.

The fact that the mean arterial blood pressure does not increase at this stage, as is the case when the minute output is increased, leads to the conclusion that the heart does not respond at once with an increased output. Blood therefore accumulates in the ventricle leading to its dilatation. The increased diastolic volume thus produced may account for the prolongation of systole.[51]

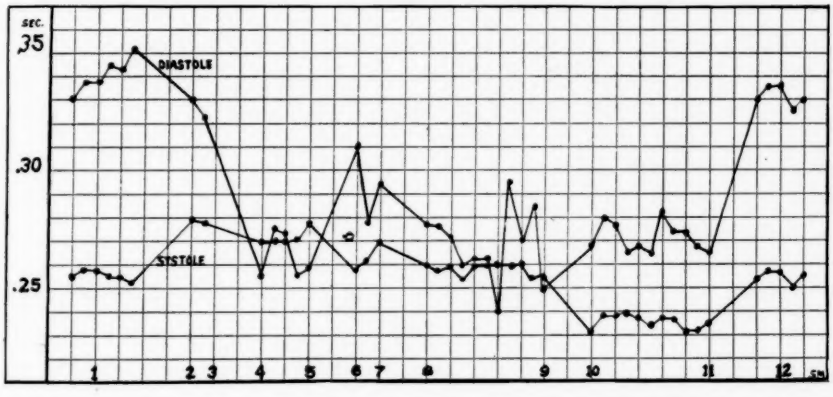

Fig. 7.—Relation of systole to diastole during various stages of saline infusion. 1—control, mean blood pressure (B.P.) 100, heart rate (H.R.) 100; 2—18th beat after injection of saline; 2-3—B. P. 110, H. R. 100; 3-4—24 beats omitted; 4-5—B. P. 103, H. R. 115; 5-6—29 beats omitted; 6-7—B. P. 110, H. R., 110; 7-8—10 beats omitted; 8-9—B.P. 124, H.R. 115, 9-10—50 beats after injection of saline stopped; 10-11—B.P. 128, H.R. 119; 12—control several minutes later B.P. 100, H.R. 100.

The mean blood pressure soon rises however showing that the heart, even in the absence of the vagi, has begun to compensate by increasing the minute output. This is accomplished in part by an increased heart rate and, perhaps, also by an increased systolic discharge. Systole during this stage continues to be longer than the theoretical values for these rates being approximately equal to the longer control cycles. The prolongation of systole chiefly affects the ejection phase, as was pointed out in reviewing the literature, and this would be an additional factor in increasing the systolic discharge.

The heart rate remains rapid and the blood pressure is maintained high for some time after the cessation of the injection, implying that the plethora induced by the rapid intravenous infusion has persisted. The duration of systole, however, does not remain prolonged but becomes equal to the theoretical value even while the heart rate and blood pressure are still affected.

As these observations show, the cycles obtained during rapid intravenous injection of saline deviate from Henderson's uniformity of behavior law.

4. *The Ultimate Effect of Altered Cardiovascular Changes on the Duration of Systole and Diastole*: In studying the effect of any influence on the temporal relation of the cardiac phases, cognizance must be taken of the temporary changes which occur while the heart is accommodating itself to the new conditions. An analysis of the temporary changes occurring in the recovery from nerve stimulation and during the intravenous infusion of saline was presented above. Similar changes may occur when any other factor associated with the cardiac cycle is modified. These temporary changes must be excluded when the ultimate effects produced by a certain influence are studied. This is not an easy task for, as under natural conditions, slight variations of systole and diastole occur also after the heart has accommodated itself to the new conditions.

In selecting the cycles to determine the end effects two criteria were used. In the first place cycles were selected which occurred a sufficient interval after the onset of the change, the number of beats excluded varying directly with the amount of departure from normal. However, in order to avoid the cycles occurring when the deviation was returning to normal too long an interval was not allowed to elapse. A second criterion depended on the amount of variation occurring in the consecutive cycles selected. The variations in these cycles were less than those occurring in successive cycles during the temporary changes. Although no arbitrary amount of variation was set yet the actual variation of the 10-15 cycles selected approximately equaled that occurring in successive cycles under natural conditions.

(*a*) *Ultimate Effect of Altered Mechanical Influences on the Temporal Length of Systole and Diastole*: As it is essential to exclude as carefully as possible any influence other than the one studied, the vagi which are the main channel for compensation were divided. For technical reasons, however, no attempt was made to exclude the accelerator nerves. The two main mechanical influences capable of modifying the cardiac action are (1) the venous pressure and (2) the arterial resistance.

(1) *Increased Venous Pressure*: An investigation of the effects of increased intracardiac volume, is of some clinical value because it may increase our understanding of the causes of cardiac dilatation. Cardiac dilatation occurs in many clinical conditions. Thus, chronic dilatation is found in many cases of chronic myocarditis, due to lues, chronic intoxications, or as the sequel of such acute infections as rheumatic fever, scarlatina, diphtheria, etc. Acute dilatations occur in many hearts during fevers, in cases with degenerated myocardiums and even in normal hearts as a result of severe unaccustomed exercise. The causes of the dilatation in these conditions are still imperfectly understood.[11, 20] These dilatations are frequently associated with an increased venous pressure.

An increase in the intracardiac volume was produced in these experiments by raising the venous pressure. The manner in which an increase in venous pressure produces the dilatation has already been discussed in considering the temporary effects of this condition. An increased venous pressure was produced by permitting saline to flow rapidly into the external jugular vein from a reservoir placed 120 cm. above the animal. Three experiments typical of all were selected (Table III) to show the response of a normal heart to a rapid increase in venous return.

The results show that systole is lengthened to a variable extent while diastole is either shortened (Exp. 3, Table III), lengthened (Exp. 2), or unchanged (Exp. 1), as a result of saline injection. When a larger amount of saline was injected irregularities of the heart beat occurred.

TABLE III

THE EFFECT ON SYSTOLE AND DIASTOLE OF INTRAVENOUS INJECTION OF SALINE (VAGI SECTIONED)

	EXPERIMENT 1		EXPERIMENT 2		EXPERIMENT 3	
	SYSTOLE	DIASTOLE	SYSTOLE	DIASTOLE	SYSTOLE	DIASTOLE
Standard	.202	.215	.21	.275	.255	.34
					.28	.33
During Injection of Saline	.227	.232	.225	.305	.27	.255
					.26	.26
After Injection	.20	.23	.21	.31	.237	.265

The variability in the response of the heart to superadded work and the rapidity of the injection modifies the amount of systolic lengthening. In the absence of the vagus control all the modifications above noted are produced either locally or through the accelerators. The local action modifying the heart rate, and perhaps slightly the duration of systole, is either determined by alterations in the nutrition of the sinus node and heart muscle or by the altered mechanical conditions produced by a change of intraventricular pressure. The main cause of the temporal lengthening of systole, however, is probably the increase in the diastolic volume and initial pressure of the ventricle produced by the increased venous pressure.

(2) *Increased Arterial Resistance*: An increase in arterial resistance occurs clinically, notably in such conditions as aortic stenosis, arteriosclerosis or compression of the aorta by a neoplasm or aneurysm. The prolongation of systole in the first condition has been clinically noticed and also shown to occur when aortic stenosis is produced experimentally (de Heer[38]). An increase in arterial blood pressure may be readily induced by compressing the abdominal aorta. This was accomplished by applying digital pressure to the aorta, the fingers being introduced through a small incision in the anterior abdominal wall. When this was done the results in most instances were not marked, inasmuch as the increased resistance thus produced was not great enough. In one case, however, when the common carotid was blocked at the same time a striking change was noted. As can be seen from Table IV the increase in arterial resistance caused a lengthening of systole although the heart rate, in the absence of vagus influence, remained the same.

TABLE IV

THE EFFECT OF COMPRESSION OF THE ABDOMINAL AORTA AND COMMON CAROTID ON SYSTOLE, DIASTOLE AND BLOOD PRESSURE (VAGI CUT)

SYSTOLE	CYCLE	DIASTOLE	BLOOD PRESSURE	
.18	.43	.25	84 m.m.	Control
.205	.42	.215	120 m.m.	During compression
.165	.42	.255	72 m.m.	After release

It follows from these observations that in normal animals with sectioned vagi as in the heart-lung preparations,[51] the duration of systole can be altered by certain mechanical factors independent of changes in heart rate.

(*b*) *The Ultimate Effect of Stimulation of the Vagus and Accelerator Nerves on the Duration of the Cardiac Phases*: The results of these experiments have already been reported in detail in a previous paper in association with Wiggers[62] so that only a summary will be presented here. The end results of stimulation of these nerves were compared with the standard curve of systole-cycle ratio established for this animal and it was found that (1) vagus stimulation increases systole and diastole, the latter more than the former, and the systole-cycle ratio conforms to the theoretical curve; (2) vagus section causes a shortening of systole and diastole, the systole-cycle ratio conforming to the theoretical line, although falling slightly below it; (3) stimulation of accelerators, both before and after the vagi are cut, causes a marked shortening of systole and diastole and the systole-cycle ratio is *very noticeably below* the theoretical values for those cycle lengths; (4) during stimulation of the vagus center by pituitary extract, accelerator stimulation causes a marked shortening of systole without any appreciable effect on diastole, the systole-cycle ratio again falling noticeably below the theoretical values.

The conclusions drawn from these observations are that the vagi have no direct effect on the ventricular muscle, the changes in systolic durations being accountable on the variation of diastolic volume at different heart rates. The accelerators, on the other hand, through some selective influence on the inherent irritability and contractility of the ventricle, exert some specific action on the duration of systole.

(*c*) *The Ultimate Effect of Epinephrin on the Duration of Systole*: So far an analysis of the effect of different single influences has been attempted. Any change that occurs in the living body, however, is the result of alterations of several factors. It is therefore desirable to determine the effect of experimentally modifying more than one influence at the same time.

Epinephrin offers a ready method of doing this. A discussion of its actions on the circulation is given by Sollmann.[16] The injection of epinephrin causes a rise of the mean arterial blood pressure by stimulating the vasomotor endings. When the vagi are intact, the rise of blood pressure stimulates the vagus center overcoming, in this way, any effect the epinephrin may have on the accelerator nerves. On sectioning the vagi, however, only the accelerator stimulation remains. The injection of epinephrin at this time produces an increase in the heart rate and a more marked rise of the blood pressure. The observations already presented in this report demonstrated that accelerator stimulation produces a marked shortening of systole and that following a sharp rise of blood pressure this period is noticeably prolonged. It is therefore interesting to see what is the final result of producing these changes simultaneously.

The result of one such experiment is illustrated in Fig. 6 of a previous report with Wiggers.[62] This figure shows that the actual systole-cycle ratio falls markedly below the theoretical curve. It is obvious from these results that under these conditions, the effect produced by epinephrin action parallels that obtained with electrical stimulation of the accelerator nerves; that is, epinephrin, through its accelerator stimulation, exerts a selective action on systole sufficient to overbalance the effect of increased resistance produced by the high blood pressure.

VI. SUMMARY AND CONCLUSIONS

The temporal variations of the cardiac phases in dogs with normal circulations were determined from optical records of the heart sounds.

It was found that under natural conditions diastole is more variable than systole. The duration of diastole depends mainly, but not entirely, on vagus tonus. The variations of systole bear no constant relation to the preceding diastole, being even less affected than diastole by the vagus tonus.

No entirely successful method of relating the duration of systole to heart rate has as yet been found. Lombard and Cope's formula, an attempt in this direction, although fairly accurate in dogs at rates slower than 150 per minute, is quite inexact at more rapid rates. An attempt to relate systole to heart rate by means of a volume curve such as Henderson's on the assumption that the heart beats according to a uniform plan showed that a different curve of this kind must be constructed for each animal.

A corollary to Henderson's conception is that the duration of systole and diastole bear a fixed relation to the heart rate. Although many of the results of other investigators may be accounted for in this way, many others are apparently contradictory.

In studying the ultimate effect of a single influence it is essential to take account not only of the many other variable influences but also of any temporary changes that may be produced.

It was found that while the heart is changing from one rate to another due to varying nervous control, the duration of diastole alters first, except occasionally, during the beginning of epinephrin or accelerator stimulation. The cardiac periods do not follow the Uniformity of Behavior law during such changes in rate. This deviation is especially marked in the recovery from accelerator stimulation during which systole is abbreviated for a long time due to a persisting selective action of these nerves.

During the rapid intravenous injection of saline, which increases the venous pressure, systole is prolonged independent of the cycle length. This is another example of a deviation from Henderson's Uniformity of Behavior conception.

The ultimate effect of mechanical influences, such as marked changes in venous pressure and arterial resistance, is the production of variations of systole independent of heart rate.

It appears from the results presented that the vagi modify the duration of systole mainly in so far as the change in heart rate produced affects the diastolic volume of the ventricle. The accelerator nerves, however, through a selective effect on the inherent irritability and contractility of the ventricle, exert a specific influence on the duration of systole.

Epinephrin, through its accelerator stimulation, produces so marked a selective action on the systolic duration that the contrary effect of the high arterial resistance is overbalanced.

Consequently the conclusions reached are: (1) the duration of systole is normally modified to a large extent by the heart rate according to a uniform cardiac action conception, such as Henderson presented; (2) other influences, however, for instance alterations of arterial resistance and venous pressure, the

specific action of the accelerator nerves and those occurring during changing heart rate and even naturally from beat to beat, are capable of producing deviations from this uniform action in an animal with a normal circulation.

VII. POSSIBLE CLINICAL APPLICATION OF RESULTS

The criterion used for diseases of the heart has changed in recent years. No longer are cardiac diseases entirely classified according to the murmur heard, but, as MacKenzie[11] has emphasized, on the functional integrity of the myocardium. It is not difficult to diagnose a case of advanced cardiac failure. However, if very much good is to be done a much earlier diagnosis is desirable. Such an early diagnosis has been worked out on the basis of dyspnea, which we are told is one of the earliest clinical signs of cardiac failure. It would be advisable for general purposes such, for example, as to determine operative or insurance risks to get even an earlier sign than this. The possibility of establishing such a sign from the durations of the cardiac phases demands further investigation.

A detailed study of the temporal lengths of these phases in recognized and suspected cardiac diseases would be interesting and desirable. It may be found, for instance, that the duration of the cardiac phases in the diseased heart as compared to the normal heart, or the comparative changes induced in these periods by measured strains would give a method of determining the functional integrity of the myocardium. Only a few of some other possible applications of such investigations are indicated below.

1. Temporary or continued tachycardia is a clinical condition so frequently observed in association with other nervous symptoms that it has come to be looked upon as due to an abnormal balance of the cardiac control exerted by the vagi and accelerator nerves. The rate sometimes becomes so rapid that it is difficult to refer it entirely to lack of vagus tone but necessitates the assumption of an accelerator stimulation. The only hopeful way of determining whether the accelerators are really involved is to accurately measure the actual duration of systole in these conditions and compare it with the theoretical value determined from the standard volume curve of the individual.

2. Physiologically the pronounced shortening of systole may be looked upon as one means of preventing an excessively high arterial pressure with increasing heart rate. Thus, in an accelerated heart there is a tendency to prevent an increased minute output not only by a decreased diastolic filling but also by an abbreviation of the ejection period. It is conceivable that if the acceleration is produced in another manner (e.g. toxic substances affecting the sinus node) such a shortening does not occur. In this case a greater strain would be thrown on the vasomotor mechanism to prevent an abnormal elevation of pressure leading in this way to a resultant persistent dilatation. Furthermore, the abbreviation of systole induced by accelerator stimulation tends to spare the ventricular muscle from the contractile stress and in this way compensates for the more frequent occurrence of systole and the shortened diastoles. It is conceivable that this sparing influence of a shortened systole is lost when the increase in heart rate is not due to accelerator stimulation. Whether this may account for or contribute to certain of the symptoms, such as result from a weakened heart associated with some types of tachycardia, remains to be seen. Of significance in

this connection are the observations of Wiggers and Clough[61] who consistently found that the period of systole was of longer duration in functional cardiac disorders (irritable hearts, D. A. H.) than in normal individuals. If the premises presented in this and in the report published with Wiggers[62] are correct, it would indicate that the rapid hearts in these conditions are not due to a hyperexcitable sympathetic system.

3. The lengthening of systole found in cases of aortic stenosis has been variously explained, as due to a compensatory mechanism of the ventricle to permit sufficient blood to flow through the stenosed opening. If the assumption that systole can be modified by the diastolic volume is correct, then the mechanism of this compensation can be readily explained, as the stenosis itself is capable of producing such an increase in the diastolic volume. The contrary statement sometimes made that in aortic insufficiency the period of systole is decreased would, on the face of it, be incompatible with this conception, as in this condition also an increase in diastolic volume occurs. However, in all such cases the shortening of systole may be explained on the basis of an increased heart rate. In any event, the methods that have been used to determine the duration of systole were too inaccurate to be very valuable. The writer is unaware of any accurate study of this problem which merits further investigation.

4. The adaptation of the heart to varying conditions is well illustrated in the response to added work. When more blood returns to the ventricle, it responds by expelling more blood, not only by a greater number of ejection periods, but also by a greater relative duration of each systole. In certain diseased conditions, however, the heart muscle is so weakened that it cannot respond to this added strain and "heart failure" ensues. Whether in these conditions the duration of systole is lengthened remains to be seen.

Many other possible clinical problems suggest themselves but the few mentioned are sufficient to show that further investigations along these lines would be of practical clinical value.

This investigation was performed in the physiology laboratory of the Western Reserve University Medical School, under the supervision of Professor C. J. Wiggers. I wish to express my thanks to Dr. Wiggers for his advice and suggestions.

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CLASSIFICATION OF STREPTOCOCCUS*

III. Streptococci from Normal and Pathogenic Throats, also from Wounds, Classified by Sugar Fermentations, Limiting Hydrogen-ion Concentration, and Reactions on Milk Mediums

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IN the former papers we have considered the classification of streptococci, based principally upon their ability to ferment certain sugars. We found the streptococci in the average person's throat to be remarkably constant in health and during attacks of acute rhinitis and pharyngitis and also during a recurrent "influenza" attack.

In the present paper, parallel with the sugar fermentations, the limiting hydrogen-ion concentration and certain reactions on milk mediums have been observed.

HISTORICAL

Broadhurst[9], Stowell, Hilliard and Schlesinger[25] and Smith and Brown[24] record a difference in the acidity produced on dextrosebouillon between strains of streptococci from human and bovine sources, the acidity being determined by titration, using standard sodium hydroxide solutions and phenolphthalein as the indicator. Ayers[4] found the limiting hydrogen-ion concentration, determined colorimetrically, of streptococci from human infections to range between P_H 5.5 and 6.0, this held true for 26 strains of the 34 tested; those strains isolated from human mouth, and from cow's milk, mouth, udder and feces had a P_H 4.6 to 4.8 limiting hydrogen-ion concentration (151 of 167 cultures). Smillie,[23] using Henderson and Palmers[14] colorimetric method for the hydrogen-ion determination, found 4 strains of hemolytic streptococci isolated from the throats of scarlet fever cases to have a limiting hydrogen-ion concentration of P_H 5.1 to 5.7 and one strain a value of P_H 4.5. The former 4 strains proved to be pathogenic for mice, the latter strain was nonpathogenic. Avery and Cullen[2] obtained, colorimetrically, a P_H 5.0 to 5.3 for 124 human strains and a P_H 4.3 to 4.5 for 45 bovine strains. Brown[8] records a P_H 4.5 to 4.6 for 12 bovine strains and a P_H 5.1 to 5.4 for 18 presumably human strains. Jones, F. S.[16] isolated 56 strains of hemolytic streptococci from milk and found that these strains fell into two main groups, 43 produced a limiting hydrogen-ion concentration of P_H 4.4 to 4.7 and 13 a lower value of P_H 5.0 to 5.2. Five cultures of the last group were tested as to their pathogenicity for rabbits, the results were all negative. Jones, F. S.[17] in another article records the limiting hydrogen-ion concentration of 7 human strains varying between P_H 5.1-5.6; 5 low acid-producing strains from milk P_H 5.1-5.8; 5 equine streptococci (4 strains isolated from the nasal mucosa and pharynx of horses suffering from influenza, 1 was cultivated from an an abscess) produced

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P_H 4.7-4.9 and 7 bovine strains (mastitis) P_H 4.6. All these four groups were grown on 1 per cent dextrose-bouillon. This author has carefully compared the titration with the colorimetric method for determining acidity of streptococci cultures upon various mediums. For the former he used 0.05 N sodium hydroxide solution. He shows the two methods to run remarkably parallel, in his hands the titration method proved a satisfactory method of distinguishing the degree of acidity of the cultures. Ayers, Johnson and Davis[5] were unable, with their dextrose-yeast-peptone medium, to distinguish between human and bovine strains by the titration method. Jones, F. S.[17] and Jones, H.,[18] have both shown that the addition of serum to plain bouillon causes the streptococci to produce more acid than when grown on plain dextrose-bouillon alone. Broadhurst[10] called attention to the fact that streptococci grown on meat bouillon produced much more acid than when grown on meat extract bouillon. Avery and Cullen[3] found that pneumococci grown on several different sugars, in 1 per cent concentration, for 18 hours, produced the same final hydrogen-ion concentration.

Brown[8] observed that salicin was fermented slower than other sugars by streptococci in his series. Jones, H.[18] has shown that there is a difference between the limiting hydrogen-ion concentration for streptococci grown for four days on 1 per cent dextrose and 1 per cent lactose bouillon. This same author after studying the effect of various medium constituents upon the limiting hydrogen-ion value of streptococci concludes in part: "The amount of glucose which a given organism can consume is influenced by the buffer content of the medium, i.e., by such constituents as phosphates, protein, etc., which aid in holding the concentration of the hydrogen-ion from the toxic limit, thus permitting a larger amount of the sugar to be decomposed. An initial reaction with a P_H well over the alkaline side has the same effect."

In reviewing the literature, it seems that the action of streptococci on milk cultures has not yielded any information leading toward a differentiation between strains of this group. Recently Sherman and Albus[22] have compared 50 strains of streptococci, isolated from milk, with 50 strains isolated from the udder by drawing the milk directly into sterile flasks. These workers lay emphasis upon the acid production and coagulation of milk and upon the reduction of certain dyes, especially methylene blue. Their Streptococcus lactis group (from milk) caused curdling of the milk and reduction of the methylene blue within 24 hours. Their Streptococcus pyogenes group (from the udder) were not so regular in their curdling action and never reduced methylene blue milk cultures. Brown[8] did not find either coagulation or reduction of methylene blue milk of any great value in differentiation of strains. He records 50 per cent of the bovine strains coagulated milk within 24 hours, and that none of the human strains caused coagulation within this time, as to the methylene blue test, the reduction was not constant for either group.

TECHNIC

With the exception of a few changes in details, the technic was the same as in our former papers.[1] The blood agar was prepared in the same way. De-Kruif and Ireland[13] have recently recommended a sheep-serum-blood cell mixture, consisting of 20 per cent serum, 5 per cent cells and agar 75 per cent. This

method is based on experimental evidence of the maximum streptolysin production. Their technic was carried out on several groups of plates. If the agar is cooled properly, the blood added slowly while the container is well shaken during the process, under these conditions we have observed the minimum hemagglutination, making a clear uniform plate. With the DeKruif-Ireland technic there is a difference in the size of the hemolytic zones, but it is a quantitative difference only, the advantage of this technic—in our hands—has not been sufficient to warrant the additional work necessary to carry through their complicated technic.

The vitamine-bouillon was prepared as in our former work. There was an initial hydrogen-ion concentration of P_H 7.8 for all bouillon cultures, determined by Barnett and Chapman's method[6] using phenol red as indicator. The growth was much better than on the bouillon adjusted to P_H 7.0. In fact growth was so much heavier after 24 hours incubation as compared with the former bouillon of P_H 7.0, that we worked some time eliminating all possibilities of contamination causing the increased amount of growth. In the proctocols to be reported in this paper there is not a single "no growth" notation.

Lactose, mannite and salicin were used in 1 per cent concentrations in the vitamine-bouillon, each being tubed in about 5 c.c. quantities. The dextrose was in the same concentration, but about 8 c.c. was put into each tube. Care was taken to see that the reaction was P_H 7.8 after the final sterilization. In view of the work done by Mudge[20] we have autoclaved all sugar mediums at 15 pounds for 15 minutes instead of sterilizing in the Arnold-sterilizer for three successive days.

The brom-cresol-purple milk was prepared according to Clark and Lubs,[11] this was used for detecting acidity and coagulation. The methylene blue milk was prepared with the same concentration of the dye as Sherman and Albus[22] recommended. We found it unnecessary to sterilize the two separately. The required amount of methylene blue can be added to the milk, then tubed and sterilized. After cooling, the tubes are shaken and the methylene blue is oxydized, giving the original colored milk solution.

In detail the technic was as follows: Swabs were directly touched to cooled and partially dried blood agar plates, then smeared well with a sterile bent glass spreader. If time did not permit or blood agar plates were not ready, the swab was immediately soaked for one minute in Holman's cooked meat medium,[15] this was always kept in the incubator ready for use. If the plates were to be inoculated within six hours, these warm Holman meat tubes were incubated, but if the material was not to be plated until the next day, the tubes were set aside and incubated for six hours just before plating. A loopful of this Holman meat culture was diluted with 5 c.c. of sterile Ringer's solution and after shaking well one loopful of this diluted suspension was plated, this was spread over the plate by means of the sterile glass spreader. If the swab was from a wound, two or more plates were usually smeared with the same spreader, after smearing the first plate, thereby getting a graduated dilution, insuring isolated colonies on the plates. These plates were inverted and incubated for twenty-four hours. The growth was described, and typical colonies were picked, in some cases 20 colonies from the original swab. The picked colonies were put on warm Hol-

man's meat medium and incubated for 6 to 24 hours, the time of incubation being of no importance so far as the morphology of the streptococci is concerned. After six or eight hours there is a good growth. These were stained, direct from the Holman meat medium, by Gram method. We have used the Weigert's gentian violet solutions, being unable to obtain the aniline sulphate for the permanent gentian violet solution as recommended by the Committee on Descriptive Charts.[21] The quick method for the Gram stain was used. All strains were classified morphologically, as to size of cocci, length of chains, appearance of the cocci in chains, i.e., if in diplococci form or single, elongated, etc. All diplococci in very short chains or appearing singly were eliminated, as so far these have been bile soluble and have added unnecessarily to the technical work. So far we have not found any of the bile insoluble strains described by Mair.[19] The streptococci proving to be in pure cultures were transferred to vitamine-bouillon, 1 per cent dextrose, lactose, mannite and salicin in vitamine-bouillon, and brom-cresol-purple and methylene blue milk, all these were inoculated from the Holman meat tube. The plain bouillon culture was used for the bile test. One drop of a 0.1 per cent alcoholic solution of the methyl red was added to each of the lactose, mannite and salicin tubes, any color from a salmon to a red was recorded as positive. Five c.c. was pipetted from the dextrose bouillon 48 hour culture into a clean test tube (150x20) one drop of an alcoholic solution of methyl red added. (We have found the amount, as recommended by Avery and Cullen,[2] 0.02 c.c. to give the sharpest end point, the pipette should be roughly standardized to drop 50 drops to the c.c.). To this is now added 10 c.c. of distilled water. A red color denotes a hydrogen-ion value of about 4.3 to 4.6, a salmon color P_H 5.0 to 5.4. These were checked with the colorimetric method, the standards being prepared according to Clark and Lubs.[12] With a little experience the color obtained by the above technic can be read off to within 0.2 P_H readily. There were a few cultures, as was mentioned by Avery and Cullen, that did not give any color at all with the methyl red indicator on the dextrose bouillon cultures, these are recorded as "irregulars" in the following tables. Several strains were found to rapidly decolorize the methyl red, first appearing as a deep red color, then after a few minutes a salmon and after 15 minutes completely decolorized to the original bouillon color. Jones[17] has observed the same action upon methyl red by some of his streptococci cultures. For this reason the methyl red was added to the sugars as an indicator for fermentation after they have been incubated. The colors were read immediately after addition of the indicator. The milk cultures were recorded after 12 hours, 24 hours and then every 24 hours for 8 days.

EXPERIMENTAL I. NORMAL AND PATHOLOGIC THROATS

One hundred thirty-nine strains of streptococci were isolated from the posterior nasopharynx of healthy persons, and from cases of acute tonsillitis and pharyngitis. There were 40 cases in all, twenty were apparently normal throats, and twenty from other than normal throats, the above diagnosis was given for the majority of these cases.

In the healthy throat series were 75 strains of streptococci isolated—42 hemolytic and 33 nonhemolytic strains.

HEMOLYTIC STREPTOCOCCI

Holman's Classification	Number of Strains	Per cent	STRAINS WITH LIMITING H-ION CONCENTRATION OF Ph.4.3-4.5	Ph.5.0-5.4	Irregular strains
Streptococcus Anginosus	21	50.	20	1	0
Streptococcus Pyogenes	17	40.5	16	1	0
Streptococcus Subacidus	4	9.5	2	0	2
NONHEMOLYTIC STREPTOCOCCI					
Streptococcus Salivarius	20	60.6	17	2	1
Streptococcus Mitis	9	27.3	8	1	0
Streptococcus Ignavus	3	9.1	3	0	0
Streptococcus Equinus	1	3.	1	0	0

Throats showing evidence of acute inflammation. 64 strains were isolated, 27 hemolytic and 37 nonhemolytic.

HEMOLYTIC STREPTOCOCCI

Holman's Classification	Number of Strains	Per cent	STRAINS WITH LIMITING H-ION CONCENTRATION OF Ph.4.3-4.5	Ph.5.0-5.4	Irregular strains
Streptococcus Anginosus	14	51.8	12	2	0
Streptococcus Pyogenes	9	33.4	9	0	0
Streptococcus Subacidus	3	11.1	2	1	0
Streptococcus Hemolyticus i	1	3.7	1	0	0
NONHEMOLYTIC STREPTOCOCCI					
Streptococcus Salivarius	22	59.5	21	1	0
Streptococcus Mitis	12	32.4	12	0	0
Streptococcus Ignavus	2	5.4	2	0	0
Streptococcus Nonhemolyticus i	1	2.7	1	0	0

These findings can be expressed in another way:

42 strains of hemolytic streptococci from normal throats:
38 strains or 90.48% would be classified as nonpathogenic, nonvirulent or bovine.
2 strains or 4.76% would be classified as pathogenic, virulent or human.
2 strains or 4.76% would not be classified (irregular).
33 strains of nonhemolytic streptococci from normal throats:
29 strains or 87.88% would be classified as nonpathogenic, nonvirulent or bovine.
3 strains or 9.09% would be classified as pathogenic, virulent or human.
1 strain or 4.03% could not be classified (irregular).
27 strains of hemolytic streptococci from pathogenic throats:
24 strains or 88.90% would be classified as nonpathogenic, nonvirulent or bovine.
3 strains or 11.10% would be classified as pathogenic, virulent or human.
37 strains of nonhemolytic streptococci from pathogenic throats:
36 strains or 97.30% would be classified as nonpathogenic, nonvirulent or bovine.
1 strain or 2.70% would be classified as pathogenic, virulent or human.

The following tables give the results of the 139 strains of streptococci on brom-cresol-purple milk and methylene blue milk.

BROM-CRESOL-PURPLE MILK.	NORMAL THROATS. HEMOLYTIC.	PATHOLOGIC THROATS. HEMOLYTIC.
Acid within 24 hrs. coagulation after 24 hours.	9 strains—21.43%	9 strains—33.33%
Acid and coagulation within 24 hrs.	10 strains—23.81%	0
Acid and coagulation after 24 hrs.	10 strains—23.81%	9 strains—33.33%
Acid within 24 hrs. No coagulation.	3 strains—7.14%	4 strains—14.81%
Acid after 24 hrs. No coagulation.	9 strains—21.43%	4 strains—14.81%
No change.	1 strain—2.38%	1 strain—3.71%

BROM-CRESOL-PURPLE MILK.	NORMAL THROATS. NONHEMOLYTIC.	PATHOLOGIC THROATS. NONHEMOLYTIC.
Acid within 24 hrs. coagulation after 24 hrs.	13 strains—39.39%	13 strains—51.35%
Acid and coagulation within 24 hrs.	8 strains—24.24%	0
Acid and coagulation after 24 hrs.	8 strains—24.24%	11 strains—29.73%
Acid within 24 hrs. No coagulation.	0	2 strains—5.41%
Acid after 24 hrs. No coagulation.	3 strains—9.09%	3 strains—8.10%
No change.	1 strain—3.03%	2 strains—5.41%

METHYLENE BLUE MILK	NORMAL THROATS. HEMOLYTIC STREPTOCOCCI.	PATHOLOGIC THROATS. HEMOLYTIC STREPTOCOCCI.
Reduced within 24 hrs. Coagulation within 24 hrs.	3 strains—7.14%	0
Reduced within 24 hrs. Coagulation after 24 hrs.	6 strains—4.28%	2 strains—7.41%
Reduced after 24 hrs. Coagulation after 24 hrs.	14 strains—33.33%	3 strains—11.11%
Partial reduction. With or without coagulation.	0	5 strains—18.52%
Reduction. No coagulation.	1 strain—2.4%	0
No change.	18 strains—42.85%	17 strains—62.96%
Reduction before coagulation. Regardless of time factor.	13 strains—31. %	5 strains—18.52%
Reduction and coagulation at same reading, regardless of time factor.	11 strains—26. %	0

METHYLENE BLUE MILK	NORMAL THROATS. NONHEMOLYTIC STREPTOCOCCI.	PATHOLOGIC THROATS. NONHEMOLYTIC STREPTOCOCCI.
Reduced within 24 hrs. Coagulation within 24 hrs.	3 strains—9.09%	0
Reduced within 24 hrs. Coagulation after 24 hrs.	2 strains—6.06%	6 strains—16.22%
Reduced after 24 hrs. Coagulation after 24 hrs.	6 strains—18.18%	10 strains—27.02%
Partial reduction. No coagulation.	1 strain—3.03%	2 strains—5.40%
Coagulation.		

METHYLENE BLUE MILK	NORMAL THROATS. NONHEMOLYTIC STREPTOCOCCI.	PATHOLOGIC THROATS. NONHEMOLYTIC STREPTOCOCCI.
No reduction.	1 strain—3.03%	0
No change.	19 strains—57.57%	18 strains—48.65%
Reduction.		
No coagulation.	1 strain—3.03%	1 strain—2.70%
Reduction before coagulation regardless of time factor.	10 strains—30.3%	10 strains—27. %
Reduction and coagulation at same reading, regardless of time factor.	4 strains—12. %	8 strains—22. %

EXPERIMENTAL II. THROATS AND INFECTED WOUNDS OF THE SAME INDIVIDUAL

One case of severe streptococci infection of a scalp wound was studied. The infection spread over the whole scalp area and down on the left side of the face and neck. Cultures were made from the posterior nasopharynx and the infected wound the day the patient was admitted, and again six days later.

The results of the first culture were:

POSTERIOR NASOPHARYNX

Streptococcus	Subacidus	8 strains	Limiting	H-ion	Concentration of	Ph 5.2 to 5.5
"	Subacidus	2 strains	"	"	"	4.5
"	Pyogenes	2 strains	"	"	"	5.3
"	Pyogenes	2 strains	"	"	"	4.3
"	Anginosus	2 strains	"	"	"	5.3
"	Ignavus	4 strains	"	"	"	5.3

WOUND

Streptococcus	Pyogenes	4 strains	Limiting	H-ion	Concentration of	Ph 5.2 to 5.4
"	Pyogenes	4 strains	"	"	"	4.3 to 4.5

The second culture (six days later)

POSTERIOR NASOPHARYNX

Streptococcus	Anginosus	2 strains	Limiting	H-ion	Concentration of	Ph 5.4
"	Subacidus	2 strains	"	"	"	5.4
"	Ignavus	2 strains	"	"	"	5.3

WOUND

Streptococcus	Pyogenes	6 strains	Limiting	H-ion	Concentration of	Ph 5.3 to 5.4
"	Mitis	2 strains	"	"	"	5.4
"	Ignavus	2 strains	"	"	"	5.4

For the past year or so we have had in mind the question of the influence of throat streptococci upon those of the wound and vice versa. We have had the opportunity of studying only a few cases. These were typed only by Holman's classification, as the Avery and Cullen method using methyl red had not been published when this was done. There were 23 cases in this series, we are giving only ten cases here, which represent the average findings. These were isolated observations, made as time permitted and without choosing special cases.

Case 200. Infected wound after removal of both breasts.

THROAT			WOUND		
Streptococcus	Pyogenes	3 strains	Streptococcus	Ignavus	2 strains
"	Hemolyticus i	1 strain	"	Salivarius	2 strains
"	Ignavus	2 strains			
"	Salivarius	2 strains			

Case 200. Six days later.

THROAT			WOUND		
Streptococcus	Mitis	2 strains	Streptococcus	Ignavus	1 strain
"	Salivarius	1 strain	"	Salivarius	1 strain
			"	Fecalis	1 strain

Case 202. Infected wound after removal of malignant growth from axilla.

THROAT			WOUND		
Streptococcus	Hemolyticus ii	2 strains	Streptococcus	Hemolyticus ii	1 strain
"	Ignavus	1 strain	"	Salivarius	1 strain
"	Salivarius	1 strain	"	Fecalis	1 strain

Case 203. Draining pyothorax.

THROAT			WOUND		
Streptococcus	Hemolyticus i	2 strains	Streptococcus	Equinus	2 strains
"	Mitis	1 strain			

Case 204. Infected gun-shot wound of arm.

THROAT			WOUND		
Streptococcus	Anginosus	1 strain	Streptococcus	Infrequens	1 strain
"	Mitis	4 strains	"	Mitis	2 strains

Case 205. Infected gun-shot wound of foot.

THROAT			WOUND		
Streptococcus	Equinus	2 strains	Streptococcus	Ignavus	1 strain
"	Mitis	1 strain	"	Salivarius	1 strain
			"	Fecalis	1 strain

Case 207. Otitis Media.

THROAT			WOUND		
Streptococcus	Equinus	2 strains	Streptococcus	Equi	2 strains
"	Ignavus	1 strain	"	Subacidus	1 strain
			"	Nonhemolyticus i	2 strains

Case 209. Pus from hip fracture of 12 months' standing in elderly person.

THROAT			WOUND		
Streptococcus	Salivarius	4 strains	Streptococcus	Nonhemolyticus i	3 strains

Case 216. Draining pyothorax.

THROAT			WOUND		
Streptococcus	Anginosus	1 strain	Streptococcus	Equi	1 strain
"	Salivarius	2 strains	"	Salivarius	1 strain

Case 217. Draining pyothorax.

THROAT			WOUND		
Streptococcus	Equi	2 strains	Streptococcus	Mitis	2 strains
"	Salivarius	2 strains			

DISCUSSION

The results of the first part of this paper seem to show that the streptococci, both hemolytic and nonhemolytic, in throats of cases of acute tonsillitis and pharyngitis do not differ, in their limiting hydrogen-ion concentration and fermentation of sugars, from those streptococci present in normal throats. Jones, F. S.[17] has isolated several strains of low-acid-producing streptococci from milk, the limiting hydrogen-ion concentration on plain dextrose-bouillon cultures ranging from P_H 5.1 to 5.8. These strains if present in the throat and having this final hydrogen-ion concentration, would fall in the pathogenic group.

In the second part of this paper the only case of wound infection, that could be classified clinically as a virulent type, which was studied in respect to the limiting hydrogen-ion concentration of the isolated streptococci, presents many interesting features. There were hemolytic streptococci present in the throat of this patient during the first part of the infection that belonged to the pathogenic group (P_H 50. to 5.3) and there were also some belonging to the nonpathogenic group (P_H 4.3 to 4.5), both pathogenic and nonpathogenic giving the same sugar reactions, this was also true for the cultures made from the wound. Six days later all the strains isolated from both throat and wound were of the pathogenic variety. A swab only comes in contact with a relatively small amount of exudate and the swabs from such wounds are usually heavily seeded, as a result only a small portion of this is used for inoculation of the respective medium, consequently there is only a very small part of the exudate examined. The position in the wound of that portion of the exudate which is examined may exert considerable influence upon the streptococci isolated, i.e., whether the superficial or deep part of the exudate is collected on the swab, or even a swab taken directly from the wound surface after removal of the exudate. These points are now being studied in this laboratory.

The results we have obtained from the milk cultures have not yielded us anything that would help toward classifying the streptococci. The action of the brom-cresol-purple milk, as to the time of acid reaction and coagulation, and the methylene blue milk, as to the time of reduction and coagulation, seemed to have been independent of the sugar fermentations and limiting hydrogen-ion concentration on dextrose-bouillon. The factors underlying the reduction of the methylene blue in the milk cultures does not seem to be clearly understood. Bartel[7] seems to think the cause of the decolorization is explained by the exhaustion of the dissolved oxygen of the milk by the activity of the bacteria and the subsequent reduction of the lactose or other constituents of the milk. Several of our strains not fermenting lactose, readily reduced the methylene blue in the milk cultures. It probably is an indicator of a certain particular form of metabolism of the strain, involving the rate of oxygen requirement by the organism and possibly a reductase formation. This question is being further studied by one of us at the present time.

The use of the 1 per cent dextrose-bouillon for the sugar medium to be used for the limiting hydrogen-ion concentration has been found to be satisfactory. We have noticed a marked difference in the hydrogen-ion concentration in the different sugars used, after 48 hours incubation. The lactose, when fermented, seems to give about the same color as the dextrose, but the salicin and mannite

were found to vary within wide limits, usually giving a lower concentration of hydrogen-ions. The dextrose-bouillon medium was not fermented by some strains, or at least the hydrogen-ion concentration did not fall within the methyl red range. All these doubtful strains are being studied now by us. With more extensive work upon this group and the strains reaching a limiting hydrogen-ion concentration of P_H 4.5 and P_H 5.0, that is the upper limit of the nonpathogenic, nonvirulent or bovine group, and the lower limit of the pathogenic, virulent or human group, there may be some more light thrown on the subject of using the limiting hydrogen-ion concentration as a means of classifying streptococci.

One should also take into consideration that the work on the throat cases here recorded was done during the past summer months. This is being continued into the coming winter months, possibly there will be some differences observed, at least a parallel series will be of interest.

SUMMARY

The technic of the simple and rapid method of determining the hydrogen-ion concentration, recommended by Avery and Cullen, has proved satisfactory in our hands.

The hemolytic and nonhemolytic streptococci found in normal and pathogenic throats were of the same varieties, when classified by Holman's sugar fermentation tests, Avery and Cullen's final hydrogen-ion concentration and their action on brom-cresol-purple and methylene blue milks.

In many cases of infected wounds, particularly those of the head and upper extremity, the same strains of streptococci were found in the throat and the wound.

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THE ETIOLOGY OF ACUTE INFLAMMATIONS OF THE NOSE, PHARYNX AND TONSILS*

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(*Continued from page 275.*)

CONCURRENT BACTERIOLOGIC STUDIES—SUMMER OF 1920

The bacteriologic methods of 1920 were essentially those of 1919 save that the baked blood plates for B. influenzæ were omitted and that the vestibule of the nose was in each case washed out before the nasal culture with cotton wet with tap water.

Results.—Four subjects were used in this study. Cultures were made daily (with a few omissions) from June 21 to July 19 from the right and left nasal cavities, the right faucial tonsil, and the posterior pharyngeal wall of two subjects, S. M. and A. G. The third, S. B. G., was similarly cultured from June 21 to June 30, inclusive. The fourth, F. J. C., was cultured only once. S. M., A. G., and F. J. C. each developed a mild coryza. S. B. G. was unaffected.

Subject S. M. showed in the nose from the outset Staphylococcus albus. On June 24 and thereafter S. aureus also was found. Diphtheroids appeared in cultures from each nasal cavity made four hours after his third intranasal experiment. S. albus remained throughout all the experiments. S. aureus was present occasionally, but, except on the days following its first appearance, in smaller numbers than S. albus. The diphtheroids fluctuated in numbers and were sometimes absent. There was no apparent relation between their numbers and the chilling.

The tonsil contained at the outset Streptococcus nonhemolyticus, pneumococcus, and S. albus. Streptococcus hemolyticus appeared in the tonsil culture taken 24 hours after the first experiment on June 22; the applicator in this experiment was on the nasal septum and the subject's mouth was closed. Forty-eight hours after the experiment, a pure culture of S. hemolyticus appeared in the tonsil culture. The number diminished on the following day to 11 per cent of all colonies, and subsequently remained present in numbers from 1 to 12 per cent of all colonies counted, through July 12. Nose and throat remained clinically normal throughout this time. Further experiments were performed upon this subject July 12, 15, and 17, with the thermopile tips respectively on the nasopharyngeal and oropharyngeal wall and in the air of the postnasal space. The proportion of hemolytic streptococci in the tonsil cultures slowly rose during this time—July 12, 12 per cent; July 14, 16 per cent; July 16 and 17, numerous, not counted; July 19, 25 per cent; July 20, 36 per cent. July 17,

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this subject began to develop symptoms of coryza. By July 19 he had cough, nasal stuffiness and rhinorrhea and malaise. Symptoms present but abated the following day. The mother of this subject had had a severe cold from about July 12; his symptoms may or may not have been connected with the experiments.

The pharynx showed Streptococcus nonhemolyticus and pneumococcus and occasionally S. albus and S. aureus. June 27, S. hemolyticus appeared and subsequently it was obtained in four cultures, each time associated with tonsil cultures containing a like organism. S. hemolyticus is so usual an inhabitant of the tonsils (Davis, 1920) that its incidence here may or may not have been connected with the experiments.

Subject A. G. showed in the nasal cavity initially S. aureus; subsequently S. albus appeared on each side. The right side showed usually a preponderance of S. albus, the left of S. aureus. No other organisms appeared in the nasal cultures.

The right tonsil showed Streptococcus nonhemolyticus throughout, i. e., from June 21 to July 19. A. G. was subject of an experiment June 21, 23, and 24; application was made on the anterior end of the right nasal septum, the anterior end of the left lower turbinate and in the left middle meatus, respectively. The symptoms of a slight rhinitis—nasal stuffiness, slight headache and slight mucopurulent discharge—developed June 24. The secretion and stuffiness persisted until June 29. June 24 two colonies of M. catarrhalis appeared on the tonsil plate and June 26 one on the tonsil and three on the pharynx plate. June 28 S. albus began to be present in the right nose. Otherwise no change in bacteriology was noted, the nose showing S. aureus and the tonsil and pharynx nonhemolytic streptococci as before. A. G. was again subject July 7 and 17, with the applicator on the right middle turbinate in the first case and with no mucous membrane application at all in the second. July 17 twenty colonies (44 per cent) of M. catarrhalis appeared on the tonsil plate. There were no accompanying clinical symptoms. Streptococcus hemolyticus appeared after the experiment of July 7, four colonies on the tonsil and one on the pharynx plate July 7, one on the tonsil plate July 8 and one on the tonsil plate July 12. These were the only appearances of hemolytic streptococci in this subject either in the series of 1919 or 1920.

In subject S. B. G. there were present in the nose S. aureus and S. albus. On the right tonsil there were S. nonhemolyticus, pneumococcus, S. aureus and S. albus. The pharynx showed S. nonhemolyticus and pneumococcus. There was practically no change in the bacterial flora throughout the period studied neither were there any signs of a cold. The cultures from the pharynx were frequently sterile and always showed relatively few bacteria, as was the case in this subject in 1919.

F. J. C., whose pharyngeal culture showed abundant hemolytic streptococci, developed a mild cold the day following his first experiment (applicator on left nasal septum). Unfortunately a contagious origin cannot be ruled out, however, for his baby brother developed a cold about the same time.

Discussion.—Streptococcus nonhemolyticus was found in all four individuals studied, pneumococcus in two, S. hemolyticus in three, and M. catarrhalis in

one. In S. M., on one occasion there was an abundance of S. hemolyticus in the tonsil cultures before and during the symptoms of cold and sore throat. In F. J. C. a cold followed a single exposure of an individual with abundant hemolytic streptococci. The appearance of M. catarrhalis in A. G. after experimentation was paralleled by a like occurrence in 1919.

INTERPRETATION OF REACTIONS TO CHILLING

It is a fact beyond question that potentially pathogenic bacteria may lead a saprophytic existence upon the pharyngeal and tonsillar mucous membranes of healthy subjects (e. g., see Davis, 1920). It is equally indisputable that those bacteria may under appropriate circumstances become the active agents of infection, local or generalized. We believe that exposure to cold may be one such exciting factor of infection. We have shown also that chilling of the body surface causes a reflex vasoconstriction and ischemia in the mucous membranes of the nasal cavity, postnasal space, oropharynx, palate and tonsils. That the latter is the mechanism by which local resistance is lowered and infection excited we have not proved. However, there would seem to be justification for advancing tentatively, at least, the hypothesis that the ischemia may mediate the infection. Jonathan Wright in the course of a discussion of the etiology of acute upper respiratory infection (1914, p. 295), the most scholarly the writer has anywhere found, says:

> "It may well be, as has been admitted, that certain bacteria are at once pathogenic when they reach the mucous membrane. Indeed, this seems very probable when they reach the mucous membranes of certain individuals. It may well be that such individuals always present, owing to systemic states, conditions of the mucosa which offer an ever-open avenue to infection; but granting all this, which indeed is in reality a part of our conception of the mechanism of the process, it seems extremely likely that local biochemical change, dependent upon molecular activities acting through the sympathetic nervous system, is the antecedent in the majority of cases of bacterial infection. This molecular disturbance of the normal activities of the sympathetic nerves may be set up by external or internal agencies, by the chilling of the body surfaces, or by derangements in the activities of the internal organs. Owing to the fact that wet feet and the chilling of distant regions of the surface of the body are, at least in clinical experience, quite as frequently followed by coryzas and sore throats as the direct impact of such external influences upon the head and neck, we have the right to infer that the shock at the surface must be transferred to internal ganglia and there translated into impulses which are carried to the surfaces of the mucosa of the upper air passages. There they give rise to the chain of biophysical and biochemical changes which may simply result in a mild coryza or a catarrhal pharyngitis, the resolution of which terminates the chain, or these conditions may be in themselves the starting point of bacterial invasion."

In the insufficient light of present knowledge, it would seem not improbable that the ischemia incident on cutaneous chilling, by decreasing cell respiration, or by retarding removal of the products of cell metabolism, or by increasing the permeability of the epithelial cell surfaces to the bacterial products, or by decreasing the local supply of specific antibodies, or by altering the media in the tonsillar crypts and folds of the pharyngeal mucosa in which the bacteria are living, or, especially when accompanied by direct chilling of the mucous membranes, by altering the state of aggregation of the colloids of the protoplasm (Schade, 1920) or by a combination of these factors, might affect the local

change postulated by Wright and thus so disturb the equilibrium between host and parasite as to excite infection. We here use the term "infection" as denoting a process separable from that of invasion or penetration of the bacteria into or through the mucosa. For study of tonsils in the early stages of infection has usually shown the crypts swarming with bacteria with none demonstrable beneath the mucosa surface (Wright and Smith, 1914, p. 291; Wright 1907; Goodale 1899). There is much collateral evidence to support the hypothesis of Wright that a factor other than any of those suggested above; namely, the surface-tension relations of bacteria and mucosa cell surfaces (1909) enters into the determination of penetration or nonpenetration of bacteria through the mucosæ. This hypothesis certainly deserves experimental investigation.

The demonstration that cutaneous chilling causes reflex vasoconstriction and ischemia in the nasal cavity, nasopharynx, oropharynx, tonsils and palate at least furnishes a new and correct point of departure for future investigation, to replace the former false assumption of congestion.

That the mechanism we have elucidated is the only one concerned in exciting the acute cold it would be obvious folly to believe. The conditions determining the equilibrium between host and parasite in the tonsillar crypts and folds of the pharyngeal mucosa must be so extremely complex that many different factors are capable of disturbing it either in the direction of proliferation of the parasites and infection or of their annihilation.

A mechanism perhaps more often responsible than ours for the acute "cold" has been elucidated by Leonard Hill and F. F. Muecke (1913). These workers found that in hot moist crowded rooms, such as ill-ventilated theatres or meeting halls, the mucous membranes over the turbinate bones and nasal septum swell, become turgid with blood and tissue lymph, and covered with a thick secretion. In such crowded places massive droplet infection is likely to occur. On going out into cold, moist, outer air, the blood vessels constrict and the nasal mucous membrane is chilled but remains swollen with tissue lymph. These authors believe—and certainly with apparent justification—that this latter condition of the nasal mucous membrane affords a suitable condition for bacterial proliferation. They find that the dangerous primary passive congestion is much less if the air in the room is kept circulating and is not overheated.

The monograph of Leonard Hill (1919) especially urges the importance in causing colds of *contagion* and of the unnatural conditions of *indoor life*, where bodily vigor is not maintained by adequate outdoor exercise, crowding favors massive infection from those already actively infected and from carriers, and overheating of the atmosphere at head level causes passive congestion of the nasal mucous membrane and predisposes to infection. In Hill's monograph is to be found detailed discussion also of the effects on the respiratory membrane of altered respiration and of changes in temperature of the inspired air, as distinguished from the phenomena we have been especially studying, namely, the reflex effects on the mucous membrane circulation of chilling the body surface without altering the quality of the inspired air. The effect of physical exertion (without excessive fatigue, of course) in increasing respiration and hence transudation of liquid through the respiratory membrane, is emphasized by Hill

as a valuable factor in the prevention of initiation of infection of the respiratory membrane.

It should be clearly borne in mind that the factors of *contagion* and of *general bodily health* are probably of considerably greater importance to preventive medicine and the welfare of the community than the effects of chilling of the body surface.

We would reiterate also in order to minimize any possiblity of misunderstanding. We are concerned in our experiments with *excessive* chilling of the body surface, which like overdosage of a useful drug, we believe may have ill effects. Certainly we would not encourage the unreasoning fear of drafts and exposure so often encountered. Good ventilation and circulating air in buildings, cold weather, and out-of-door living are needed for vigorous health; many people are unquestionably benefited by cold bathing. But excesses in this direction should also be avoided.

We are now in a position to outline an explanation for the annual cold-weather increase in incidence of upper respiratory diseases, which, although admittedly incomplete and in part speculative, would yet seem to fit well the known facts. With the beginning of cold weather, cessation of summer and autumnal out-of-door life, and beginning of hot air and steam heating, conditions of living for the average American and European become less favorable to general health and resistance. Opportunities for excitation of autoinfection by prolonged or excessive chilling become more frequent, as do those for cross-infection in crowded cars and meeting places, where mucous membranes are rendered more susceptible to infection by the close, hot atmosphere (Hill and Muecke, 1913). As the bacteria gain foothold and multiply on one after another susceptible mucous membrane it is in harmony with known immunologic facts to suppose that they tend to increase in virulence and so add another factor to the general tendency to increased prevalence of respiratory infection. With moderation of the weather and return to out-of-door life in the spring, aided possibly by some as yet unknown cyclic or other change in the bacterial invaders, we would expect the annual decline in prevalence. (Jour. Am. Med. Assn., 1920, lxxv, 1500.)

How practically to escape respiratory infection in so far as possible? Lead a vigorous and healthful life with adequate sleep, food, exercise and fresh air. Bathe daily. Keep the houses sufficiently warm to be comfortable, but not, as most American houses are in winter, overhot and overdry. Avoid contagion from infected persons, remembering that respiratory diseases are communicated chiefly through droplets of mucus sprayed into the air through coughing, sneezing or speaking. Avoid excessive irritation of the mucous membranes by tobacco smoke or other vapors. Avoid prolonged or excessive chilling. Avoid crowding in hot atmospheres. Obstructions to breathing or foci of infection if present should of course be removed. Some degree of "hardening" to exposure, graded and adapted to the needs of the individual, we believe is possible, and of the greatest service. As one valuable factor in this process, one of us at least after some eight years trial is convinced of the efficacy in his own case of a daily morning shower bath with warm water concluded with a few minutes of very cold water.

IV. ANAPHYLACTIC "COLDS"

The discussions of vasomotor rhinitis and of asthma in the majority of the current texts will have to be entirely rewritten. The rescue of these affections from the nebulous province of diatheses and neuroses, their establishment upon a definite and sound, if not wholly complete, etiologic and therapeutic basis, makes up one of the chapters of modern experimental medicine upon which one's imagination lingers with most satisfaction. Since, however, thoroughly modern and adequate treatments of this subject are available (v. Goodale, 1918, and Walker, 1919) they will not be further discussed here beyond pointing out a subgroup of cases recently come within the experience of workers in the field, which simulate recurrent common acute colds.

I cannot do better than quote briefly from Dr. Walker (1919, p. 146):

> "It is not at all uncommon for some patients to complain of what they call hay fever symptoms or very frequent head colds throughout the year. Since this kind of case seeks aid from the nose specialist, who terms the condition vasomotor rhinitis, the internist sees little of the condition, and even when the internist does see the case first he immediately refers it to the nose specialist. In the future, however, such cases should be tested for sensitization to proteins. Not infrequently are the emanations of animals the cause of these all the year hay fever symptoms. Horse hair dandruff and cat hair are frequently the cause of these spasmodic attacks of hay fever, which last a few minutes to a few hours or even a day or two, and in such instances the patient gives a positive skin test with the proteins of the hair. Less often the injection of various foods causes spasmodic attacks of short duration simulating hay fever. True seasonal pollen cases frequently complain of frequent head colds throughout the year and these head colds closely simulate short attacks of hay fever. In some of these pollen cases the sensitization serves to permanently render the mucous membranes extremely sensitive and irritable, so that sudden temperature changes, drafts, odors, and dust particles, are sufficient to produce symptoms, in other pollen cases bacteria seem to be the cause."

See also Goodale (1916), Floyd (1920), and Walker (1920). The important point here for the laryngologist, internist and pediatrist to remember is that frequently recurring "colds" may have protein sensitization as their basis and to be in readiness to do the skin tests when indicated.

V. ACUTE INFLAMMATION DUE TO SYSTEMIC, TOXIC AND NEUROTIC FACTORS, TO MECHANICAL AND CHEMICAL IRRITATION, TO EXTREME LOW TEMPERATURES, AND TO NASAL OBSTRUCTION

A discussion of the etiology of acute inflammation of the nose, throat and tonsils should at least give passing mention to various inflammatory conditions of the upper respiratory tract associated with more general affections. Acute rhinitis occurs as a local prodromal symptom of influenza, measles, scarlatina, whooping cough, enteric typhus, small-pox, chicken-pox, secondary or congenital syphilis and glanders. (Thomson, 1913, p. 113.) Similarly for acute pharyngitis. Diphtheritic and gonorrheal rhinitis occur; also that of erysipelas.

Acute upper respiratory inflammations may be set up in those exposed to local irritants, as millers, furriers, sawyers, tobacco-workers, ivory and steel turners, and decorators, or (Schade, 1920) when the mucous membranes are exposed to extreme low temperatures. Locally the vapors of formalin, the halogens, ammonia and the fuming mineral acids and dust and coal and tobacco

smoke may give rise to them. A destructive form of rhinitis may occur in workers in bichromate of potash, mercury, arsenic or osmic acid. Acute pharyngitis not infrequently follows traumatism, as the swallowing of hot fluids, corrosives, hot condiments, raw spirits, and the impaction of foreign bodies. It may be induced by operations on the pharynx with much sponging or traction on the tissues, e.g., enucleation or morcellement of the tonsils. Secondary infection may, of course, aggravate any such primary condition.

Acute mucous membrane inflammation may occur in connection with the administration of certain drugs, as potassium iodide, arsenic, mercury and antimony.

Acute rhinitis "is predisposed to by all obstructive affections of the nose and postnasal space. Chronic hypertrophic rhinitis, deformities of the septum, polypi and chronic empyemata conduce to the contraction and exacerbation of acute nasal catarrh; and frequent and persistent rhinitis in children is generally due to nasopharyngeal adenoids. Indeed, a large majority of children who are reported to be always catching a 'cold in the head' will be found to possess inflamed or overgrown pharyngeal tonsils." (Thomson, ibid.)

A vasomotor turgescence of the nasal mucous membrane may originate in certain individuals from some reflex, such as chilling of the feet, sudden exposure to bright light or damp air, inhalation of vitiated air, gastric disorder, or sexual irritation.

VI. CONCLUSIONS

The following causes of acute inflammation of the pharynx, tonsils and nose are recognized in the present dissertation:

1. The filterable virus of Kruse and Foster, inducing apparently a clinical entity, a type of acute coryza. According to the experiments of its discoverers, this is of relatively high virulence and may cause infection practically independently of the action of exciting factors.

2. Various bacteria, including the Pneumococcus, Streptococci, B. rhinitis, B. diphtheriæ, Friedländer's bacillus, B. influenzæ, and probably also M. catarrhalis, B. septus, M. paratetragenus, S. aureus, and possibly others seem to be capable of inducing infection of variable extent, duration and symptomatology. The relative virulence of the microorganisms also varies within wide limits—both between themselves and from time to time in the same organism—in some instances high, infections of epidemic proportions, largely independent of exciting factors, may be produced; in other instances low, sporadic infection may occur only when some factor or factors serve to depress resistance, general or local, to the point of vulnerability.

3. Protein sensitization, the basis of vasomotor rhinitis and of true bronchial asthma, the underlying cause also of a relatively infrequent sub-group of acute recurrent "colds."

4. Various systemic diseases, drugs, mechanical and chemical irritants, chronic nasal affections and reflex neuroses.

One factor by which resistance to bacterial infection may be lowered is excessive chilling.

Experiments by many workers have shown that animals whose blood temperature is lowered may have decreased resistance to infection. This, however,

is probably not the mechanism by which chilling excites the common upper respiratory infections in man.

Experiments have shown that chilling of the body surface of animals causes congestion of many internal organs. Reasoning from a faulty analogy, the theory has been evolved and made widely current that similar congestion occurs in the upper respiratory mucous membranes of man when chilled, and is responsible for the local lowering of resistance. However the work of the present authors has shown that the opposite is true, namely, that chilling of the body surface causes reflex vasoconstriction and ischemia in the mucous membranes of the nasal cavity, postnasal space, and palate, oropharynx, nasopharynx and palatine tonsils. It seems not improbable that the ischemia may be the means of lowering local resistance. In other instances the mechanism of Hill and Muecke, i. e., crowding in overheated places followed by emergence into a cold atmosphere, is doubtless responsible for colds.

During the course of the experiments by which the vasoconstrictor reaction to chilling has been demonstrated, some ten cases of cold or sore throat, usually mild, have appeared among the subjects. In a number of instances the clinical symptoms were accompanied by interesting bacterial changes.

It is a pleasure to thank the friends without whose generous aid as subjects much of the present work would not have been possible.

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THE RELATION OF PATHOLOGISTS TO THE INSTITUTIONAL PRACTICE OF MEDICINE*

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THE paper is presented to this body of scientists as one of a series which has the following objects:

1. To show pathologists (including bacteriologists, serologists, immunologists, and other workers in pathology) the economic part which they should play in the practical consideration of patients.

2. To show clinicians that laboratory investigators can, and sometimes do, play an important rôle in the practice of medicine.

3. To assist in bridging the gap which now exists between what has been called pure science and its practical application to patients.

4. To suggest the great probability that some of the most important fields of scientific research may be found in direct connection with the study of patients.

5. To relieve the minds of young aspirants in research from the conception that the most fundamental research must of necessity be carried on in isolated research institutions.

The following facts have been the stimuli for this series of reports:

1. Intimate, valuable correlation of laboratory and clinical facts and methods is being practiced in some large medical and surgical clinics.

2. Such correlation is unfortunately rare on a large and significant scale in most large and small hospitals throughout the country.

3. There is a demand for such correlation because the writer weekly receives letters from hospitals requesting aid.

4. There is a great dearth of pathologists to fill these positions, a fact which is leading practical clinicians to have girls trained to do laboratory work under their own imperfect direction.

5. The writer has seen much inefficient laboratory work by poorly and inefficiently trained girls and interns. The work of many such poorly trained workers discredits a science which you and I desire to see maintain its high place of true usefulness.

6. Many professors of pathology throughout this country manifest a lack of interest and an abundance of indifference in the practical application of their science to clinical practice.

Table I shows what is being done by one institution in the application of laboratory methods to the practice of medicine.

It may be seen that each patient averaged 3.72 laboratory reports, each of which usually entails many examinations or tests.

*Presented before the American Association of Bacteriologists and Pathologists, New York, April, 1920.

TABLE I

LABORATORY EXAMINATIONS OF 60,645 PATIENTS

Determinations of the basal metabolic rate	5,650
Gastric analyses	11,946
Other clinical laboratory tests	192,739
Electrocardiographic records	2,021
Fresh tissue examinations	12,964
Necropsies	465
Laboratory reports	225,785

Ninety-nine and two-tenths per cent of the patients were alive when the examinations were made; examinations were made on 0.8 per cent at necropsy, and 97.7 per cent of the patients were living at the time the reports were made.

These data actually show what the active pathologist can do and is doing in the practice of medicine. It would be impossible, at present, to state what percentage of patients was actually benefited by these examinations, but it may be stated accurately that all reports had positive or negative value in establishing a diagnosis and that the diagnosis governs the therapeutic measures. The functions of the pathologists who were responsible for the 225,785 reports may be divided as follows:

1. Confirmation of diagnoses, of which the clinician might have had some suspicion.
2. The diagnosis of conditions which the clinician did not suspect.
3. The recognition of accessory pathologic conditions.
4. The correction of clinical diagnoses.
5. The confirmation of positive clinical diagnoses.
6. The determination of stages in the course of disease.
7. The determination of the physical status of the patient preparatory to possible operation or other treatment.
8. Assistance in determining the extent of operations.
9. Determination of data for preoperative, operative and postoperative prognosis.
10. Determination of the cause of death in nonsurgical and in surgical cases.
11. Determination of the cause of death due to incorrect medical or surgical judgment.
12. Determination of the cause of death resulting from incorrect operative technic.
13. Assistance in determining causes and modes of surgical infections.
14. Assistance in clinical, surgical, and laboratory research.
15. The actual treatment of disease.

I shall not attempt to analyze the relation to the patient of metabolic rates, gastric analyses, electrocardiographic records, bacteriologic and serologic examinations herewith presented. This must be left for some future time. But there is one field in pathology worthy of consideration in detail and one with which I am more intimately familiar, that is, the field of tissue pathology. Most pathologists study material at necrospy and hence see end

results; some have occasion to examine tissue from living patients for diagnostic purposes. It is this group of pathologists in whom I am at present especially interested because most of them are not pursuing their vocation to the fullest extent of their practical capacity. They are pathologists but they are not clinicians practicing pathology as a specialty in association with patients. This field of possible activity of such pathologists is illustrated in Table II.

TABLE II

SPECIMENS OF TISSUE EXAMINED DURING 24,368 OPERATIONS

	SPECIMENS	DIAGNOSIS POSSIBLE ONLY WITH A MICROSCOPE
	HOSPITAL A (GENERAL SURGERY)	
Breast	289	18 (6.2 per cent)
Extremities	118	20 (16.0 per cent)
Gall bladder	1,086	0
Genitourinary organs	486	33 (6.7 per cent)
Head	33	17 (51.0 per cent)
Intestines	249	32 (12.0 per cent)
Lip and glands	44	6 (13.0 per cent)
Neck	259	54 (20.0 per cent)
Stomach	191	61 (31.0 per cent)
Thyroid	1,638	4
Trunk	153	31 (20.0 per cent)
Uterus (portion)	165	11 (6.0 per cent)
Uterus (entire)	655	21 (3.0 per cent)
Tubes	625	4
Ovaries	601	5
Parovarian cysts	75	0
Specimens for diagnosis	432	207 (47.0 per cent)
	HOSPITAL B (GENERAL SURGERY)	
General specimens	2,635	461 (21.0 per cent)
	HOSPITAL C (EYE, NOSE, AND THROAT)	
Diagnostic specimens	461	432 (93.0 per cent)
	CLINICAL OFFICES	
Diagnostic specimens	586	558 (95.0 per cent)

Twelve thousand nine hundred sixty-four fresh tissue examinations showed that 21.3 per cent of all registered patients (60,645) presented surgical specimens. More than 40 per cent of all the registered patients came to operation and more than 57 per cent of all patients operated on furnished pathologic specimens.

Diagnosis of many pathologic conditions can be made before operation; some can be diagnosed during surgical exploration before tissues are removed; and still more can be diagnosed grossly after tissues are dissected and removed; but there is a certain percentage which cannot be diagnosed positively grossly and must be submitted to microscopic examination. This method of diagnosis was of necessity applied to 15.2 per cent of all specimens in the series, although the percentage varies from 15 per cent to 25 per cent from year to year. The total percentage not only varies but the percentage on different organs and tissues varies from year to year. However, in a series of records covering

30,130 specimens from all sources, 21 per cent were of necessity examined microscopically.

The real value to the patient cannot be seen from this total percentage, but may best be seen from examining the character of certain special examinations. Thus it may be seen that 2,279 specimens (series of 800, 432, 586, and 461, respectively) were removed for diagnostic purposes, which means that 3.7 per cent of all registered patients received one form of direct preoperative and operative aid from the tissue pathologist. While this is perhaps the most important function from the standpoint of the patient, the act of picking up incorrect clinical and surgical diagnoses during operation is of just as great importance. This function will be considered in a future paper. Sufficient data are already at hand to justify the statement that incomplete operations and incorrect prognoses are avoided by virtue of the activity of a clinical pathologist working in conjunction with appreciative surgeons who lay no claim to being either great macroscopic or microscopic diagnosticians. The clinician's diagnostic efficiency has already been described in another article of this series. It was seen in a comparative study of clinical preoperative instructions and pathologic findings that the clinician is correct in 95 per cent of cases when he makes positive diagnoses, but experience has taught him that positive diagnoses are frequently dangerous, detrimental to his reputation, and productive of injustice to the patient. While this percentage is high, it has been pointed out, for example, that 22 per cent of all carcinomas of the breast seen in the surgical laboratory are actually discovered by the pathologist and that when the clinician makes a questionable diagnosis of a malignant condition in the breast he is correct in 49 per cent of the cases in so far as malignancy is concerned. Thus it may be seen that the tissue pathologist has a great function which he is capable of exercising, and that microscopy is just as essential to clinical diagnosis, in practice, as in auscultation, palpation, and other methods of physical examination. It is not only an accessory, it is an essential. Therefore, the expert microscopist is an essential factor in clinical diagnosis.

LABORATORY METHODS

THE DIAGNOSIS OF TYPHOID AND PARATYPHOID INFECTIONS*

By Henry J. Goeckel, Phm.D., Cranford, N. J.

IN a previous paper[1] attention was called to the early diagnosis of typhoid and paratyphoid infections by the identification of the bacteria in the urine with high titer agglutinating serum. The agglutinating method was first used in an attempt to determine if motile rod bacteria, frequently encountered in urine with pus, were of the typhoid-colon group, without resorting to cultural methods. The diagnostic value soon became apparent. Since the last publication the method has been applied successfully in ways not anticipated at that time.

The cases previously cited indicate that the blood count if relied on to verify the physical diagnosis is at times very misleading, especially when the Widal reaction is negative.

The classic Widal reaction is today a questionable test on which to rest a diagnosis of typhoid infection, as is done by many physicians. Beside the late appearance of a positive blood test in many cases, it has in recent years been demonstrated that homologous agglutinins not only exist for all the members of the typhoid-colon group of bacteria, but likewise for these and for gonococci.

We must also take into consideration that there are probably ten million people in the United States who either through typhoid infection, or by prophylactic immunization have developed or been sensitized to agglutinin production. This agglutinin production persists over long periods of time. Consequently we are liable to get a positive Widal reaction in low dilutions of serum where an active typhoid infection is not present, thereby possibly misleading rather than aiding in the diagnosis.

It has likewise still to be shown whether a gonococcic infection can reactivate or bring about an increased production of the homologous agglutinins in a typhoid-paratyphoid sensitized person when a gonococcic infection exists. This is being investigated by one of our staff.

In the dilutions of the high titer agglutinating serum employed no cross fixation is obtained.[2] This has been demonstrated on pure cultures and various mixtures of the same by the writer.

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*From the Clinical and Pathological Laboratory of Muhlenberg Hospital, Plainfield, N. J.

[1]Goeckel, H. J.: Jour. Lab. and Clin. Med., January, 1920, v, No. 4.

[2]Titer of serum employed was typhoid, 1-5000; paratyphoid A and B, each 1-10,000; B. coli, 1-2000. These were used respectively in 1-2500, 1-5000 and 1-1000 dilutions.

I have recently employed this method on the bacteria of fresh feces from suspected cases. A selected particle of the feces was suspended in physiologic salt solution, thoroughly agitated to break up all clumps. Solid material was allowed to settle and the bacterial suspension was diluted to the usual turbidity employed for the hanging-drop Widal test.

In one of the two feces examined a recognizable clumping and inhibition of motility for typhoid bacilli was given, and in the other for paratyphoid, type B. A dense clumping was secured in each case with the baccillus coli agglutinating serum and none with the paratyphoid, type A. serum. This application apparently affords another ready means of recognizing the presence of such bacteria in case no blood or urinary bacteriemia is found at the time of examination. It likewise affords a means for promptly passing on the bacterial content of the feces in convalescing cases, making many of the bothersome cultural examinations unnecessary.

The following case history shows that a typhoid bacteriemia can be found in the circulating blood and in the urine at the same time in an acute typhoid infection:

Child, L. M., (Dr. W. M.) May 27, 1919, aged sixteen months. Throat swab and culture show a few staphylococci.

Blood.—Hemoglobin 69 per cent, index 0.622; red cell count 5,580,000; white cell count 4,800, polymorphonuclear leucocytes 43 per cent; eosinophiles 2 per cent, azurephiles 1 per cent; lymphocytes 40 per cent (large 30 per cent, small 10 per cent). Red cells normal except for hemoglobin content. Noticeable number of gram-negative rod bacteria present on the blood slides.

Urine.—Acid, distinct trace of albumin, distinct acetone test, moderate number of slightly clumped leucocytes and considerable gram-negative rods which type for bacillus typhosus.

In the following case the urinary bacteriemia was the only definitely confirmatory finding.

Child E. A., (Dr. J. V.), Aug. 26, 1920, age nine years. Persistent temperature, otherwise no physical symptoms of note. Child robust, bright and apparently comfortable. Typhoid suspected. Three experienced physicians made a thorough physical examination and could detect nothing of note. Three negative Widal tests reported by the state laboratory.

Aug. 26, 1920. *Blood.*—Red cell count 4,740,000; white cell count 11,600; polymorphonuclear leucocytes 63 per cent, mononuclear leucocytes 14 per cent, lymphocytes 23 per cent (large 10 per cent, small 13 per cent); no plasmodia.

Urine showed considerable pus and motile rod bacteria, which type for bacillus paratyphosus, type B.

The following case was an unsuspected typhoid infection:

Mrs. B. M., (Dr. F. H.) April 9, 1920, Cystitis. Frequency in urinating, discomfort in pelvic region. Passed blood in the urine. Had typhoid in 1907 and "almost died from it."

April 9, 1920. *Urine.*—Catheterized, considerable pus, no tubercle bacilli.

April 12, 1920. *Urine.*—Catheterized, considerable pus, no tubercle bacilli, but numerous motile rods which type for bacillus typhosus. This specimen had been placed in the incubator overnight.

April 20, 1920. *Urine.*—23 hour lot—sp. gr. 1.020, trace of albumen, urea 1.7 per cent, squamous epithelium, considerable pus, and bacillus typhosus, no tubercle bacilli.

May 25, 1920. *Urine.*—Sp. gr. 1.036, no albumin, urea 2 per cent, no pus, etc., urine culture—negative.

June 4, 1920. Widal reaction on blood was negative.

The following case was an emergency operation which gave no typhoid history:

Mrs. G. (Dr. P. Z.) March 13, 1920, aged twenty-five years, admitted for ruptured ectopic pregnancy which showed a rupture in uterine half of the left tube. Abdomen filled with free blood and clot.

Patient had always been in good health. One and a half years previous had an early (2 or 3 month) abortion. Two days before admission was taken with sudden violent pain in abdomen, accompanied by great shock and deathly palor. Morphine relieved pain. Another attack on morning of admission, was extremely weak, P. 144, R. 124, T. 101°F.

Before operation and after an intravenous injection of 700 c.c. of saline the hemoglobin was 60 per cent and the urine showed a sp. gr. 1.030, very faint trace of albumin, small amount of pus and a moderate number of uric acid crystals. Immediate recovery from operation was satisfactory, P. 120-144, T. 99.5 to 101°F.

March 13 and 14. Patient vomited a good deal, March 14 quite tympanitic but no pain.

March 15, 1920. A. M., slightly irrational; 9 to 10 P. M. irrational, talks incessantly.

March 16, 1920. Same, not much relieved by medication, etc. Gas and feces escaping freely.

March 17, 1920. *Urine,* sp. gr. 1.020, reaction neutral, faint trace of albumin, trace of acetone, few casts, considerable pus.

March 18, 1920. *Urine.*—Trace of albumin and of acetone, considerable pus and many motile rod bacteria.

March 19, 1920. Wildly delirious, very restless, screams. Urine, especially obtained at 3 P. M., strong albumin and strong acetone tests. Moderate number of hyaline and few granular casts, and numerous pus cells. The specimen was turbid throughout with motile rod bacteria. Upon standing these still formed a film throughout two-thirds of the specimen. They were identified by agglutinins as bacillus paratyphosus, type B. Patient died at 9 P. M., complete autopsy refused. Exploration of the operative area showed no peritonitis or wound infection. Death due apparently to a paratyphoid toxemia.

SUMMARY

The high titer agglutinating serum can be employed to demonstrate the presence of typhoid and paratyphoid bacilli in feces both for diagnostic purposes in suspected typhoid infections and to determine their presence in the feces from convalescing cases without resorting to cultures.

The typhoid bacilli can appear in the urine at the same time that an extensive circulatory bacteriemia exists, before a positive Widal reaction is obtainable. The finding of the bacilli in the urine may prove the only definite means of establishing a definite typhoid diagnosis.

A typhoid bacillus cystitis can apparently exist without producing an agglutinin production in the blood.

A typhoid or paratyphoid bacteriemia unsuspected in an operative case may prove disastrous to the patient. This paper and the previous one show that the detection and identification of motile bacilli in urine can prove of considerable diagnostic value.

THE ROUTINE DETERMINATION OF CREATININE AND ACETONE IN URINE*

By Henry J. Goeckel, Phm.D., Cranford, N. J.

NEVER having noted the inclusion of a creatinine determination in the usual routine clinical analysis of urine by others, the following modification of a recognized test as used by the writer may be of value. It gives a roughly quantitative creatinine determination without much additional labor and requires no special apparatus.

REAGENTS

1. A saturated aqueous solution of sodium nitroprusside. This keeps for a week or more when placed in an amber glass bottle. 2. A sodium hydroxide solution. 3. Glacial acetic acid.

To a row of test tubes, approximately 5 c.c. (mils) of each urine is added in consecutive order. Ten drops of the nitroprusside solution are then added to each tube followed by sufficient sodium hydroxide solution (a few drops) to produce the maximum intensity of red color.

A dense cherry red color indicates a normal or high creatinine content, while a paler shade will indicate a low content. This must be noted at once as the color begins to fade in the course of a few minutes. By examining a series of urines they can be readily contrasted. Those which appear low in creatinine content are noted.

Glacial acetic acid is then added to each tube to determine acetone. In the absence of acetone, when the creatinine is normal or low, the urine returns to approximately its normal color. Should the creatinine be high, various shades of green will become evident. When the creatinine content is very high a deep blue precipitate will form.

The presence of acetone will be indicated by the usual production of various shades of red when the glacial acetic acid is added.

This application of the acetone test to indicate creatinine affords a ready means to differentiate between those nephritic cases showing probable creatinine retention and those which are not so far advanced. It also affords a ready means in conjunction with the other routine tests for detecting surgical cases liable to be very poor risks, due to advanced nephritic conditions. It is of service in hospitals not fortunate enough to have the proper facilities and technician service to perform the more extended and reliable quantitative blood tests.

I use this test as the principal factor for advising against an operation when the creatinine is low. On the other hand I have yet to note a case showing a slight albuminuria and few or no casts, but with a normal or high creatinine content which did not pass through the anesthesia and operation uneventfully as related to the nephritis. I have seen many such cases which returned to normal following operation.

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BENIGN TUMORS OF THE GASTROINTESTINAL TRACT*

By Edward E. H. Boyer, Ph.D., Columbus, O.

THE finding of benign tumors in the gastrointestinal tract is quite unusual, and frequently very interesting and important. The least important of such neoplasms are probably those in the stomach, since the chance for obstruction to the canal is less here than in other portions of the gut. The small intestine, especially the ileum, appears to be the seat of benign growths more frequently than any other part of the alimentary tract; and the appendix gives rise to tumors less frequently than any other part. The principal types of benign neoplasms are, in order of frequency, myomata, lipomata, adenomata, fibromata.

Sometimes such growths give rise to no symptoms, and are found by accident during operations for other conditions, or at autopsy. In some cases the symptoms are very indefinite and misleading, especially if the tumor is growing toward or beyond the serosa. But when definite symptoms appear the patient usually complains of obstinate constipation, less often of intestinal hemorrhage. The constipation in such cases may be due to intussusception, but is more likely to be caused by obstruction of the lumen due to the presence of the tumor which has grown toward or beyond the mucosa. A diagnosis probably has never been made.

Sometimes the tumors grow into and obstruct the lumen; but others may progress outward to the serosa. Those of the former case, obviously, are the ones which cause most pain and discomfort, and are usually more dangerous to the patient.

Among the factors which may be responsible for the direction of growth of the neoplasm are (1) point of origin of the new growth, (2) mechanical resistance of adjacent layers, (3) biologic resistance of neighboring cells, (4) intestinal stasis.

The symptoms may simulate those of malignancy in the affected part, so that the prognostic value of these neoplasms should not be overlooked. The following two case reports are appended:

Case 1.—Service of Dr. Brock. A farmer, aged sixty-five years, was admitted to Mt. Carmel Hospital on account of pain about the umbilicus. There was no history of injury to the abdomen. The patient had had "stomach trouble and indigestion" for years, but was seldom constipated until two years ago, when violent catharsis was used. The patient has not defecated for five days. There has been considerable pain in the epigastrium, with abdominal distention. Patient has vomited stercoraceous material several times. Physical examination reveals nothing of further importance. At operation a tumor of the ileum was removed. An end to end anastomosis was performed.

Pathologic Report.—The piece of intestine measures 8 cm. in length by 2½ cm. in diameter. In the central portion there is a moderate bulging. On section one finds the lumen obstructed by a firm nodule which is pedunculated to the intestinal wall. This nodule measures 2 cm. in diameter. It is covered with mucous epithelium, and is circumscribed but not encapsulated. On section the cut surface presents the appearance of muscle tissue.

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Grossly the muscle fibres appear to originate in the muscular layer of the gut. Histologically one finds the tumor covered with a layer of simple columnar epithelium which has not atrophied. The muscle fibres run in all directions, sometimes wavy, sometimes in straight bundles, and occasionally in whorls. There is a moderate amount of connective tissue stroma. Capillaries are few, and round cell infiltration is absent. The gut, on both sides of the point of origin of the neoplasm, is of normal appearance. Just below the pedicle, however, the muscular layer thickens, loses its normal orientation, and grows toward the mucosa. The new growth is readily seen to have pushed the mucosa before it, not penetrated through it, as it grew into the lumen of the intestine. The connective tissue of the mucosa and the muscularis mucosæ are not included in the covering of the tumor; only the epithelial layer is left. It is probable that the connective tissue and muscle cells became atrophied by pressure, and only the epithelial cells were able to regenerate rapidly enough to keep pace with the progressive growth of the tumor. The structure of the tissues is very beautifully demonstrated by using Van Gieson's picrofuchsin stain.

Diagnosis.—Leiomyoma.

CASE 2.*—Female, aged fifty-two years. Complained of pain in the pelvic region. At various times she complained, also, of digestive disturbance with some gastric pain. A clinical diagnosis of ovarian cyst was made. At operation an ovarian cyst was found and removed. During exploration of other abdominal organs a mass was found, by palpation, on the greater curvature of the stomach, about three inches above the pylorus. It seemed to penetrate the entire wall of the stomach. Section was made, and the tumor was removed in one mass. The remaining parts of the viscera were apparently normal. The patient made an uninterrupted recovery.

Pathologic Report.—The mass measures 3½ x 2½ x 2½ cm. The peritoneal surface is smooth, of light color, and discloses occasional blood vessels. It was pedunculated, the pedicle measuring ½ x ¼ cm. On section one finds a mass of firm, fibrous tissue involving the entire specimen. The tumor is encapsulated, the capsule measuring ½ mm. in thickness. The cut surface exhibits a pearly translucent appearance. The cells appear to be arranged in wavy bundles and in whorls, and there is a resemblance to the cut surface of certain uterine myomata. Microscopically one finds many fibroblasts evenly distributed throughout the neoplasm. The collagen fibrils are quite numerous, and a few fibroglia fibrils are also found. The cells are grouped in bundles which lack definite orientation and are in many different planes and directions. Blood capillaries are not especially numerous, and are evenly distributed. The endothelial lining is prominent in some vessels, the individual cells appearing swollen. In other areas the endothelial cells appear flattened. There is a diffuse lymphoid cell infiltration which is not particularly marked except in some perivascular regions. A few plasma cells are mixed in with the other cells. There are no areas of hemorrhage, and degenerative changes cannot be found. One looks in vain for muscle and epithelial cells.

Diagnosis.—Fibroma of the stomach.

*This case was from the service of Dr. Shumaker, Dover, O.

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EDITORIALS

The Route of Absorption of Inhaled Substances

SOME months ago the valuable work of Blake and Cecil on experimental pneumonia was reviewed in these pages. These investigators produced typical lobar pneumonia in monkeys by injecting broth cultures of pneumococci into the trachea; they also produced bronchitis and bronchopneumonia by similar injections of influenza bacilli of exalted virulence. They concluded from studies of an animal killed three hours after pneumococcus inoculation, that primary tissue invasion took place through the walls of the larger bronchi near the root of the lung, rather than through the alveolar walls. Pneumococci were most numerous, and the beginning tissue changes most pronounced, in the peribronchial tissues around the hilum. They do not deny the possibility of invasion through the alveoli, but feel that the objective findings did not support this view.

Winternitz, Smith, and Robinson have called attention to a possible error or complicating factor in the interpretation of such experiments, when the technic is such as to involve trauma, especially to the submucosa of the trachea. Apparently this possibility cannot be excluded when such trauma exists. Moreover, it must be recognized that pneumococci, which are capable

of producing lesion of the bronchial mucosa, may invade it readily, while other organisms and substances fail to do so.

The experiments of Mullin and Ryder, carried out last year in our research laboratory at Colorado Springs, and recently published, seem to provide examples of invasion which is chiefly, if not entirely, through the alveolar epithelium. They allowed rabbits to inhale suspensions of finely divided carbon (India ink) and of virulent human tubercle bacilli. These fluids were dropped into the nasal fossae with a pipette, and allowed to run back into the pharynx, whence they are inhaled, owing to the rapid breathing and inefficient laryngeal control of these animals.

Two rabbits received an emulsion of tubercle bacilli. They were killed after seven weeks, and both showed massive tuberculous infiltration of the upper and middle lobes of the right lung, with moderately advanced tuberculosis of the bronchial nodes. The cervical nodes, spleen, and mesenteric nodes were all negative both grossly and microscopically. The parenchymatous character of the lesions, and the involvement, in both cases, of the whole of the apical and middle lobes of one lung, without other visible lesions, favors a primary alveolar process rather than a peribronchial one, but of course is by no means conclusive.

The evidence from the rabbits that were given India ink is more impressive. Free ink was found all along the respiratory tract. In every instance there was very extensive blackening of the parenchyma of the lung, with moderate to marked discoloration of the bronchial nodes. There were slight to considerable amounts of carbon in the spleen and traces in the kidney. In no case was any found in the mesenteric nodes. The aspect of the lungs was very striking, some lobes being entirely black, others showing clusters of large black blotches, while others were hardly discolored at all. "The appearance of all this pigmentation, its overwhelming quantity, is absolutely distinct from spontaneous anthracosis, which in rabbits is seldom grossly visible in the lungs, and if so occurs only as fine stippling, never as masses or blotches."

In order to exclude all possibility of absorption from the digestive tract, "Rabbit 4 was given about 3 c.c. of India ink at one time and killed half an hour later. Autopsy showed much ink in the nose, mouth, pharynx, larynx, esophagus, trachea and bronchi. The stomach was filled with vegetable material and this was blackened over a radius of about 2 cm. around the esophageal opening, but there was no discoloration below this sharply defined level in the digestive tract, the remainder even of the stomach contents being free from ink. The lungs showed almost complete blackening of the left upper lobe, and marked blackening of the left lower and right middle lobes. The bronchial nodes showed marked hyperemia and a moderate amount of carbon scattered through them. The cervical and mesenteric nodes were negative. The presence of carbon all along the inhalation route, with its complete absence from the intestine, completes the proof that the lung findings are due to inhalation."

Microscopic sections of the lungs in several animals "showed carbon in the smaller bronchi and indicated that the blackening of the lungs was

lobular in arrangement, the alveoli being packed with carbon, much of which had been taken up by large phagocytic cells, evidently the alveolar cells of the lungs; and the deeper structural tissue of the lungs contained many of these cells apparently travelling along the lymphatics." "The behavior of these cells in this instance, as well as their proliferation in acute and tuberculous pneumonia, emphasizes their close relationship to the fixed endothelial cell and the large mononuclear leucocyte. They seem readily to engulf particles which arrive on their surface, and to proliferate under the stimulus, become detached, and either to be cast off in the expectoration or taken up and carried along the course of lymphatic absorption. The cells of the upper respiratory mucous membrane, on the other hand, do not appear to be phagocytic, but rather to throw off foreign particles by means of their secretion."

The authors here follow Sewell's interpretation as to the origin of the intraalveolar phagocytic cells. In view of the work of Foot on inhalation tuberculosis, it seems likely that these cells really arise from the endothelium of the capillaries in the alveolar walls, and migrate rapidly into the air spaces under the stimulus of foreign particles arriving there.

Foot, whose work complements that of McJunkin on endothelium, injected water-proof India ink intravenously to produce vital discoloration of all endothelial cells, both fixed (vascular and sinusoidal) and free (large mononuclears), and observed carbon-bearing cells in the capillaries of the alveolar walls, escaping into the air spaces, and lying free in the bronchi. These cells phagocytosed carmine granules and tubercle bacilli injected into the trachea. He says, "These cells . . . play the principal part in the reaction to the tubercle bacillus in the air-borne infection and are evidently the cells which Sewell thought to be epithelial." In inhalation tuberculosis he finds the first site of lesions in the alveoli. Desquamation of carbon-free alveolar cells and exudation of carbon-bearing endothelial cells occur together, and both types of cell may contain tubercle bacilli. The first formation of definite tubercles occurs almost simultaneously in the alveoli and in the interstitial tissue.

Similarly, Gardner finds that the alveoli first give evidence of lesion after inhalation of Type R1 tubercle bacilli, and of granite dust.

In the microscopic sections from the lungs in Mullin and Ryder's animals, we do not find carbon-laden cells in any quantity in the bronchial mucosa, as we should expect to do if these structures were readily capable of absorption, and this is true even when the animals were killed a short time after inhalation, when the small bronchi as well as the alveoli are seen to be full of carbon. So far as the evidence of these experiments goes, the normal bronchial mucous membrane apparently does not absorb. Possibly the peribronchial findings of Blake and Cecil may be due to the concentration of bacteria originally absorbed from the alveoli and converging down the lymphatics to the hilum, as described by Krause, rather than to absorption through the bronchial walls in the immediate vicinity.

Some recent observations of our own, not yet reported, may be worth mentioning here. In a study of certain phases of guinea pig anatomy and

their bearing on experimental tuberculosis, we injected India ink into the spleens of normal pigs. If the injection is massive enough, some of the ink reaches the lungs by way of the vena cava, heart, and pulmonary artery, and is found scattered through them in endothelial cells both fixed and free. These carbon-bearing cells are numerous in the alveolar walls, but very rare in the air spaces, and there is no proliferation or desquamation of alveolar epithelium. A good many of the pigmented cells are found along the peribronchial structures, the route, that is, of the vessels which bring the carbon to the lungs and of the lymphatics which take it up and carry it to the bronchial nodes, where it is found in considerable amount. Carbon-containing endothelial cells, both fixed and free, are found in the bronchial mucosa all the way from the trachea to the smallest bronchi, and many of them seem to be passing between the epithelial cells into the lumen, where they occur with moderate frequency. In Mullin and Ryder's animals, though the small bronchi were often choked with carbon and carbon-filled phagocytes, discolored cells were virtually absent from the bronchial mucosa.

In short, carbon particles reaching the free surface of the bronchial mucous membrane from the air do not appear to be absorbed; while on the contrary, carbon particles reaching this membrane by way of its circulation seem in part to be eliminated through it. The function of absorption is vested in the alveolar, not the bronchial, epithelium, yet the latter may be the site of primary lesion and early absorption in the case of a virus especially adapted to attack it.

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—*G. B. W. (C. T. R.)*

Complications of the Arsphenamine Treatment of Syphilis

ONE of the interesting aspects of syphilology is that which deals with the so-called organotropic action of the Treponema pallidum. It has been some years since the possibility was expressed that there were different types of treponemas which were responsible for different syphilitic manifestations, for instance tabes or other nervous forms of disease were due to one type, the neurotropic; hepatic manifestations were due to an hepatotropic type, and so on. The converse also is possible that the localization of spirochetal infection is not due so much to the organotropic action of the infecting organisms as to the organic susceptibility of the tissues of the body to the spirochetes. It is

possible that the reasons for organic localization of the organism causing syphilis are the same as those concerned in the localization of the streptococci of Rosenow. However that may be there is in the literature the account of the seven glass blowers, all of whom developed labial chancres from the same infected source. Five of these developed tabes and two general paresis. Also there are the cases of Morel-Lavallée—five men infected by the same woman. One of these developed syphilitic meningitis, two, general paresis, and one, a syphilitic psychosis. Fischl reports three cases of icterus which he believes give evidence of a hepatotropic variant of the spirochete. In one case, a woman, the jaundice followed a course of antisyphilitic treatment but disappeared under further treatment; in the second case, the husband of the first, jaundice developed and disappeared before treatment was commenced. The third case, one from which the husband had contracted the disease also had jaundice during treatment.

The main reason for separating such cases from other ones in which icterus presents itself lies of course in the common source of infection. Jaundice itself is not excessively rare.

Strathy, Smith and Hannah call attention to 47 cases of hepatic complications of treatment (jaundice, or atrophy) in 8 of which a fatal issue occurred. In such cases the onset of symptoms was seldom earlier than five weeks after cessation of arsenical treatment, and these symptoms are referred to the arsenic rather than to the benzol group of the drug used. Ffrench after calling attention to the fact that, in his experience, toxic jaundice is rare, expresses the belief that there are two types of jaundice in early syphilis; one which often occurs before arsenical treatment, and is syphilitic in nature and due to the action of Tr. pallidum on the liver cells; the second, which develops toward the end of the course of arsenical injections, he attributes to the action of the arsenic. Nicaud reports 8 cases of early, and 16 of late icterus which complicated arsenical treatment. In one case the disturbance appeared after the first injection. The date of the infection, or the dose of the drug, seemed to play no essential rôle.

The fact that these cases are so rare when one considers the large number of cases who undergo treatment, leads one to suspect that the fundamental cause lies rather in the condition of the liver at the time the drug is administered. It is conceivable that somewhat the same conditions exist as those which account for the necrosis following chloroform anesthesia. Furthermore, it seems as though many of the severer cases of jaundice follow the combined use of arsenic and mercury, a fact which accentuates this conception.

This matter of toxic reactions that appear during or after treatment—especially the intravenous—with arsenic preparations is discussed by Parnell and Fildes upon the basis of their experience with the intensive treatment with neosalvarsan (neokharsivan and novarsenobillon). Most of the cases were suffering from early syphilis and all were, except for their infections, healthy. There were 1,250 patients treated, and each received a course of six doses of 0.45 grm. given intravenously at two-day intervals. Parnell and Fildes separate the toxic reactions which they believe are due to the drug

itself from the so-called endotoxic reactions which, they say are invariable to a greater or less extent after the first and occasionally after the second injection in cases of early untreated syphilis. These reactions consist of pyrexia, which usually starts six hours after the injection, and may be accompanied by a chill or headache and nausea. The cause of this is, they say, to be found in the "syphilis toxin" which is suddenly liberated from the treponemas by the destructive action of the drug. They also exclude what they call "water fever," which is due to impure water, and which consists in a fever starting very shortly after the injection.

The symptoms upon which the authors place emphasis are pyrexia, skin lesions, headache, suffusion of the eyes, vomiting, edema, pain, herpes, rigors, delirium, coryza, nausea, jaundice, albuminuria, dryness of throat, air-hunger, salivation, cyanosis, biliuria, and a number of other minor ailments. Pyrexia, skin lesions, headache and suffused eyes both in point of incidence. The skin lesions were mostly erythematous or macular in type. Symptoms of any type occurred in but 55 of the series of cases, and for the most part they were exceedingly mild. Considering the potency of the drug and the number of patients in whom it was used, the number of complications is almost negligible.

In connection with this matter of ill effects of salvarsan it is of interest that in the Report of the Medical Research Committee, the causes are assigned to (1), toxicity of the drug; (2), errors in technic; (3), susceptibility of the patient; (4), causes unknown. Our own opinion is that given a standard preparation of the drug, and a good technic, including testing of the ampoules by immersion in alcohol before using them, the main cause is a personal susceptibility of the patient. If the drug is administered by the gravity method, then an essential part of the technic includes careful preparation of the rubber tubing.

The Committee gives hemophilia, Grave's Disease, Addison's disease, lymphatism, syphilis of the central nervous system, cardiac disease (especially myocardial), aneurysm and arteriosclerosis, severe pulmonary disease, hepatic disease, gastric and intestinal catarrh, renal disease, alcoholism, acute septic conditions and constitutional tendency to skin diseases, as calling for caution in the use of arsphenamine. As danger signals during treatment they give loss of weight, headache, insomnia, loss of appetite, appearance of renal symptoms, stomatitis, diarrhea, jaundice, and erythema. Still more information, statistically speaking, is obtained from the committee of German physicians whose report is reviewed by Meirowsky. This report deals with 13,000 injections with old salvarsan, 40,954 of sodium salvarsan, 171,826 of neosalvarsan and 64,500 of silver salvarsan. Out of the total injections of old sodium and neosalvarsan there were 12 deaths attributed to the drug (1 in 18,815); but as some of the fatalities might have been avoided by more careful precautions the chance of death is put at 1 in 56,445 (1 in 13,000 with old salvarsan, 1 in 20,000 with sodium salvarsan and 1 in 162,800 with neosalvarsan). When the dose of neosalvarsan exceeded 0.6 the deaths rose to 1 in 3000, hence the committee recommend that 0.6 be the maximum dose. Encephalitis and dermatitis were more liable to occur after an overdose.

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—*P. G. W.*

Are We in Danger of Typhus Fever?

WITHIN the past few weeks there has been great excitement concerning cases of typhus fever which have reached New York. One would think from reading the newspapers that this is the first time this disease has within recent years found its way into our country. This is by no means true. In all probability New York City has never been entirely free from typhus fever. A few years ago it was demonstrated that Brill's disease is typhus fever. There is no evidence, so far as we know, that there have been secondary cases among citizens of this country. It is a fact that typhus fever has been permitted and is still being permitted to seep into this country both from Mexico and Europe. The following is an illustration of what has happened recently, what probably is happening now, and what quite certainly is likely to be repeated in the near future:

In the early part of July, 1920, Mrs. Doba Fischler, age sixty, and her son-in-law, Mr. Efroim Schachter, age thirty-one, left their home in a small village in Poland; after spending a few weeks in Warsaw, about two weeks in Paris and one in Havre, they boarded the Steamer La Savoe on August 21, taking steerage passage. They landed in New York on the thirtieth and disembarked at Ellis Island on the thirty-first. They say that they were sick for two days before reaching New York. At Ellis Island they were deloused, but the fact that they were ill was apparently not recognized. They reached Flint, Michigan, September 1, and at that time were quite ill. The physician called to see them made an immediate diagnosis of typhus fever and they were placed in an isolation hospital. Mrs. Fischler died on September 8. Mr. Schachter recovered and was discharged from the hospital on September 27. There can be but little doubt that these people received their infection on board the steamer.

Boyd and others showed before the War, at least before we got into the War, that typhus fever occasionally finds its way from Mexico into the very heart of the United States. Evidently, the United States Public Health Service, which usually does splendid work, has failed and is failing and may continue to fail, to keep typhus fever out of our country. If this be due to lack of authority, Congress should be asked to confer upon this Service more authority. If it be due to lack of funds, Congress should be asked for larger appropriations. With the splendid work that this Service has done in the past we are not going to believe that the seepage of typhus fever into this

country is due to lack of alertness on the part of the U. S. Public Health Service.

It seems to be quite generally believed that the introduction of typhus fever into this country is a matter of no great importance and that there is not the slightest possibility that it may gain a foothold in our land. We are not so sure about this. When we sent soldiers to Europe in 1917-1918 it was found that a large percentage of the negroes from the South and of the foreign element from the North was lousy, and even today, especially in cities where the foreign population is large, there are thousands of lousy people. Typhus fever can be kept out of the country. The Public Health Service can do this. If the Public Health Service fails, the people have a right to know why it fails. —*V. C. V.*